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Thromboembolism in the Cat

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During this presentation a variety of cats will be presented with thromboembolism. The acute treatment and long term goals for management will be given along with guidelines for assessment and the controversies regarding treatment addressed. There are several major points to remember in discussing thromboembolism in the cat (1) most commonly these cats have underlying cardiac disease that is frequently substantial, (2) approximately half of the cats seen with thromboembolism have clinical signs of congestive heart failure and this needs to be considered in the prognosis and treatment, (3) treatment of thromboembolism in the acute phase can be very challenging if reperfusion injury occurs with survival dependent on meticulous monitoring and careful treatment, (4) long-term treatment to decrease the reoccurrence of thromboembolism is controversial as to the drug choice and dose, and (5) despite the likelihood of severe heart disease, difficulties in treating the acute syndrome, costs and management issues and the unknowns about the correct long-term treatment for both the cardiac disease and to prevent another embolic event, enough cats survive for enough time to make the care worth the effort when the owners understand the problems.

Thromboembolism occurs most commonly as the result of cardiac disease in the cat with a clot lodged in the distal aorta and iliac arteries. The arterial occlusion per se is not the cause of the reduced circulation, but the effects of the thrombus causing a cascade of vasoconstriction events that reduce collateral circulation (believed to be more important than any clot growth). Thus, it is not primary channel blockade that causes the ischemic neuromyopathy. The cat has many collateral vessels to call upon from the vertebral arterial system, but when this fails to happen the clinical syndrome ensues. Additionally, it is the reopening of these collateral vessels in the 12 to 24 hours after the thromboembolic event that result in the reperfusion injury that kills many cats.

Thromboembolism occurs when blood stasis, endothelial damage and increased coagulation develop. Endothelial damage is present in cats with cardiomyopathy. When subendothelial collagen is exposed von Willebrands factor, which is an adhesive protein, activates the adherence of platelets to the damaged subendothelium. These activated platelets release adenosine diphosphate (ADP) which causes the release of thromboxaneA$_2$ from the platelet membrane. Thromboxane A$_2$ causes vasoconstriction and recruits more platelets to form a clot. The normal endothelial cells around the damaged area synthesize and release prostacyclin (PGI$_2$) which acts to restrict further clot growth. The platelets in the clot provide sites for procoagulant enzyme complexes to activate secondary hemostasis (intrinsic and extrinsic coagulation cascade) for the formation of the fibrin plug. This complex cascade involves the activation of serine proteases to form cross-linked fibrin in the final common pathway. Factor X is the reactant in the common pathway, where after activation (Xa) a complex with Factor Va, calcium and phospholipids are catalyzed by Platelet Factor III to transform prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin and contributes to factor XIII’s role in causing the cross-linked fibrin plug.
To counteract or balance the clotting process an inhibitory system is also present. Antithrombin III, a circulating anticoagulant, is the major plasma inhibitor of the serine proteases (destroys action of thrombin). Antithrombin III is produced in the liver and the endothelium and is the most important physiologic inhibitor of thrombin. Additionally, protein C-protein S is an inhibitor of coagulation because it limits the size of a thrombus by inhibiting fibrin generation and it increases fibrin dissolution. Plasmin which exists in the plasma as the proenzyme plasminogen is activated by plasminogen activator and urokinase-type tissue activator. Plasmin cleaves fibrin to counteract clot formation. Understanding these mechanisms is vital to the logical selection of drugs to treat and prevent thromboembolism. Also, we must seek the answer to the question of why cats are so much more prone to this disorder than dogs. It has been reported that cats have inherently higher platelet reactivity and that their platelets are larger with greater storage for agonists. Some cats with cardiomyopathy may have platelets that are reactive to ADP and this is a risk factor for thrombosis. Elevated serotonin levels have been reported in cats which increases the risk for coagulation (serotonin is released from platelets and causes vasoconstriction). Additionally, some cats may have high levels of homocysteine making them more prone to a hypercoagulation state.

Ischemic neuromyopathy is characterized by both functional and structural alterations. The insult of ischemia-reperfusion injury is caused by oxygen free-radicals causing lipid peroxidation and influx of calcium into the cells. It may be that the free-radicals damage the endothelial barrier and the endoneurial contents. In contrast to the heart and brain, the peripheral nerve is relatively resistant to structural ischemic changes because of the low energy needs, high energy stores, ability to adapt to anaerobic metabolism, and extensive anastomoses. The skeletal muscle is more susceptible to ischemic-reperfusion damage than the nerve. Although structural ischemic changes in the nerve are delayed compared to the muscle, electrophysiologic changes can occur early with evoked nerve action potentials and fast axoplasmic flow lost after 30 minutes of complete ischemia. However, recovery can occur if restitution of blood flow occurs, but in some studies is irreversible after approximately 6 hours. In contrast, a recent study in cats (Korthal 1996) demonstrated that nerves can still survive beyond this time depending on the timing of the onset of severe ischemia. In this study the nerve fibers did not have ischemic change until 5 hours post-thromboembolism compared to muscle damage 2 to 3 hours later. Consequently, some flow needs to return to prevent permanent damage. To know of partial return of blood flow is difficult to appreciate clinically, although Doppler examination or perfusion studies can at times give this information. Most commonly however, time is what tells the veterinarian of the amount or return of adequate blood flow.

Pathology of ischemic myopathy affects the cranial tibial muscle to the greatest extent although the gastrocnemius muscle can be severely damaged. Clinically the muscles become very firm because of a rigor mortis effect. The muscle experiences a depletion of ATP and this causes the muscle to contract because this is the lowest energy state for the sarcomeres. Relaxation requires ATP. When autolysis occurs the muscle proteins breakdown and the muscles soften at about 36 hours. Also, reperfusion can contribute to the return of the relaxation state, although edema at this time can contribute to keeping the legs stiff. Focal necrosis, myophagia, internal nuclei, architectural changes and infiltrates are present with some hypertrophic fibers present as compensation from surviving myocytes. Damage to the muscle in addition to the neuropathy causes the clinical signs. The neuropathology includes Wallerian-type degeneration and paranodal demyelination (affected successive nodes not random as in demyelinating neuropathies). Depending on the severity of the reduction in blood flow, the recovery of limb function that occurs in some cats within a month of the thromboembolism may be due to the repair of the myelin sheath in the demyelinated fibers. Remyelination could occur in this time frame, whereas effective regeneration would take longer. The basal lamina which is usually left intact serves as a guide for regenerating fibers.

Thromboembolism may be the first clinical sign of cardiomyopathy in many cats. Clinical signs include both the direct consequences of thromboembolism and the associated cardiace disease: acute rear limb paralysis, pain, depression, or dyspnea. The majority of cats have both rear limbs affected, although a single limb (rear or front) can be embolized. Occasionally, a cat may have paresis, rather than paralysis (paraplegia) if affected to a lesser degree. The physical examination of cats with aortic thromboembolism might include (1) the absence of femoral pulses, (2) firm to hard cranial tibial and gastrocnemius muscles, (3) pale to black cold foot pads, (4) absence of deep pain response, (5) absence of limb motion below the upper thigh, (6) hypothermia, (7) lack of anal tone and distended bladder, (8) abdominal pain if the mesenteric artery also has been embolized, (9) tachypnea and tachycardia (seen with cardiovascular compromise, stress or pain), (10) bradycardia or irregular cardiac rhythm, (11) heart murmur or gallop sound, or (12) varying degrees of depression.

As with most diseases, the severity of the disease and the resulting clinical presentation are variable. Clinical signs that indicate a ‘better’ prognosis include pad color that is pale pink, tail movement, good anal tone, upper thigh muscle control, normal mental acuity, eupneic, and normal body temperature. Also, cats have a better prognosis if they have hypertrophic cardiomyopathy and not restrictive cardiomyopathy. In addition, left atrial size affects prognosis with severe dilation being more detrimental. The prognosis is worse if congestive heart failure is present.

The diagnostic evaluation of the cat with thromboembolism includes echocardiography, thoracic
radiography, serum chemistry, electrocardiography, and blood pressure. Echocardiography will reveal the type of cardiomyopathy, the severity of the hypertrophy or fibrosis, systolic and diastolic dysfunction, size of the atria, presence of pleural effusion, and presence of atrial blood stasis or clots. Thoracic radiography permits the determination of pulmonary edema or pleural effusion. Pulmonary edema can exist even if not suspected from the auscultation of the lungs. Moreover, tachypnea is seen in the majority of these cats. The cause can be either pulmonary edema, pain, or both. The radiograph helps to determine if treatment for fluid retention is required. Azotemia, hyperglycemia, elevation in muscle enzymes (creatinine phosphokinase, aspartate aminotransferase and alanine aminotransferase), hyperkalemia, acidosis, hyperphosphatemia, and hypocalcemia can be documented. Azotemia is usually due to poor perfusion to the kidneys and it is this same mechanism that explains the hyperphosphatemia. Hyperglycemia is believed to be due to two factors: stress and increased lactate. Stress causes an increase in adrenergic hormones that inhibits insulin secretion and this in turn causes the increase in blood glucose. Also contributing to the stress response are high glucagons and cortisol levels. Concomitant with this is that lactate levels are high due to muscle anaerobic glycolysis. Lactate is a major gluconeogenic precursor to cause hyperglycemia. It is believed that insulin resistance is likely not responsible for the hyperglycemia in cats. Muscle enzyme elevation particularly that of creatine phosphokinase can be dramatic in cats with thromboembolism due to the muscle necrosis. Poor renal perfusion accounts for the hyperphosphatemia, but again the death of muscle serves as a source for massive quantities of phosphorus. The excessive phosphorus binds to calcium and this accounts for the hypocalcemia. Metabolic acidosis develops in response to the lactic acidosis reaching levels that demand specific treatment. All of these biochemical alterations change over time after the thromboembolic event. The ideal situation is for them to return to normal; however, it is important to particularly watch the potassium concentration as it can increase as reperfusion develops. Electrocardiography is vital on admission not only for the evaluation of the rhythm, but to ascertain the electrocardiographic evidence of the potassium concentration. Frequently, the ECG on admission is normal, but once reperfusion begins (as early as 6 hours after thromboembolism) the potassium concentrations can elevate quickly. Monitoring of the ECG provides a means to monitor the serum potassium level. Attention should be paid to the P wave, S wave and T wave. Most frequently cats will develop S waves, the P wave flattens and the T wave flips to positive as an indicator that the potassium is increasing. It is vital that the serum potassium be rechecked so that treatment can be started early enough to be of benefit. Severe abnormalities in conduction and rhythm progress as the potassium levels increase. Although the blood pressure determination in the hindlimbs will not be accurate, an assessment from the forelimbs is important to gauge the overall status of the cat.

Treatment of thromboembolism is an example of multitasking, changing problems, and shifting goals. It is important to realize that the specific treatment is dictated by the amount of time that elapses after thromboembolism. The discussion of treatment will be divided into four stages: (1) Immediate treatment (0 to 6 hours post-thromboembolism), (2) Reperfusion treatment (6 to 18 hours post-thromboembolism), (3) Early recovery from thromboembolism (18 hours to 7 days post-thromboembolism), (4) Long-term management (home care)

Immediate treatment. The initial problems encountered in cats with thromboembolism and cardiomyopathy might include (1) respiratory distress because of pulmonary edema, (2) cardiovascular shock, and (3) pain and anxiety. In the ideal situation the thrombus would be removed within 4 hours, but this is not going to happen because the cats cannot usually survive the surgery and the availability of the procedure is uncommon. Also, it would be ideal if the clot could be treated immediately with a clot ‘buster’ early such that the amount of cell death is decreased to decrease the problems of reperfusion injury. Again, the proper method, drug, and talent to offer this treatment is usually lacking in veterinary medicine. The most contemporary drug used for the latter purpose is tissue plasminogen activating factor (TPA).

For years the use of heparin in acute thromboembosis has been purported in the acute situation. We need to all consider the evidence for this treatment and its value. We actually do not have any evidence of its effectiveness in improving the state of these cats. Heparin (unfractionated heparin) is a heterogeneous combination of heparin molecules with disaccharide units of varying lengths. The length of the molecule affects the action. The different size heparin molecules bind in different ways and affect the coagulation in varying degrees. Also, unfractionated heparin has a high affinity to binding with serum protein and cells. Once these are loaded the heparin binds to thrombin (Factor IIa) and form a thrombin-antithrombin-complex that is irreversible. Unfractionated heparin inhibits both Factor Xa and Factor IIa. Inhibition of Factor IIa requires the long sugar residues found in unfractionated heparin and these are not found in the low molecular weight heparins (LMWH). After treatment with heparin it is possible because of the purported decrease in antithrombin III that there is a hypercoagulable period, but we do not know if such a time actually exists in cats. The unfractionated heparin dose in the cat is 100 IU/kg given subcutaneously and repeated at 6 hour intervals after a loading dose of. The efficacy has not been evaluated.

Recently LMWH have been professed as better than unfractionated heparin. These heparins are more uniform in their size with fragments of 4 to 8 kDA with an average chain length of 15 subunits and 80% < 40 subunits, this is in contrast to the heterogenous mixture of 10 to 100 subunits for the unfractionated heparin. The LMWH are short and bind primarily to Factor Xa and not to Factor IIa. It is may be that this
Hyperkalemia, acidosis, azotemia, cardiac rhythm and conduction problems, shock, and compromised cardiac function. Pulmonary edema must continue to be treated as demanded in cats that suffer from this in addition to the thromboembolism. The clinical signs of reperfusion include depression, arrhythmias, conduction disturbances, and in general, ‘crashing.’ ECG monitoring permits notification of changes in serum potassium levels. Additionally, monitoring of the serum potassium levels every 2 to 4 hours may be required when possible. Knowing when the potassium concentration is increasing and acting on this situation early is key to success. Acidosis will develop in these cats and contribute to the hyperkalemia. The aggressiveness in the treatment of hyperkalemia depends on its severity. Treatment can include modest fluid therapy with NaCl (careful to watch for pulmonary edema), intravenous glucose (but if the cat is already hyperglycemic this is not effective), sodium bicarbonate (effective for the acidosis too), very low doses of insulin (give with glucose and monitor), to intravenous calcium (directly counteracts the cellular effects of hyperkalemia). Always during the selected treatment the potassium concentration is monitored for effectiveness of treatment and to be alerted to the time to stop treatment. This is important because overshooting treatment past the reperfusion period will result in hypokalemia. Frequently, specific treatment for the heart disease such as ACE inhibitors is not given at this point in the treatment of these cats. Azotemia can be mild to severe depending on the cardiac status, underlying renal reserve, renal perfusion, presence of renal emboli, severity of reperfusion, doses of furosemide required to control pulmonary edema, and fluid administration tolerated to assist during reperfusion. Monitoring blood pressure, heart rate, respiratory rate, mentation, and renal perfusion continue to be important. Pain relief at this stage of the disorder usually is not required.

Reperfusion injury. Cats will suffer from reperfusion injury to varying degrees depending on the vascular hyperpermeability, hyperkalemia, edema and acidosis present. In some, there will be no apparent consequences while in others this is the cause of death. The problems to battle in this stage of treatment are hyperkalemia, acidosis, azotemia, cardiac rhythm and conduction problems, shock, and compromised cardiac function. Pulmonary edema must continue to be treated as demanded in cats that suffer from this in addition to the thromboembolism. The clinical signs of reperfusion include depression, arrhythmias, conduction disturbances, and in general, ‘crashing.’ ECG monitoring permits notification of changes in serum potassium levels. Additionally, monitoring of the serum potassium levels every 2 to 4 hours may be required when possible. Knowing when the potassium concentration is increasing and acting on this situation early is key to success. Acidosis will develop in these cats and contribute to the hyperkalemia. The aggressiveness in the treatment of hyperkalemia depends on its severity. Treatment can include modest fluid therapy with NaCl (careful to watch for pulmonary edema), intravenous glucose (but if the cat is already hyperglycemic this is not effective), sodium bicarbonate (effective for the acidosis too), very low doses of insulin (give with glucose and monitor), to intravenous calcium (directly counteracts the cellular effects of hyperkalemia). Always during the selected treatment the potassium concentration is monitored for effectiveness of treatment and to be alerted to the time to stop treatment. This is important because overshooting treatment past the reperfusion period will result in hypokalemia. Frequently, specific treatment for the heart disease such as ACE inhibitors is not given at this point in the treatment of these cats. Azotemia can be mild to severe depending on the cardiac status, underlying renal reserve, renal perfusion, presence of renal emboli, severity of reperfusion, doses of furosemide required to control pulmonary edema, and fluid administration tolerated to assist during reperfusion. Monitoring blood pressure, heart rate, respiratory rate, mentation, and renal perfusion continue to be important. Pain relief at this stage of the disorder usually is not required.

Early recovery from thromboembolism. Near the end of the reperfusion period the limbs can swell, sometimes dramatically. The skin can become erythematous and pitting edema can develop. Cats can loose the hair over the limbs. If a cat survives the reperfusion injury it is critical that the entire cat be reevaluated because the furosemide dose, quantity of fluids, specific treatment for hyperkalemia, and pain...
treatment all will need to be adjusted or eliminated. This is also the time that the monitoring of the physical state of the cat must not stop. Immediately after the intensity of treating a cat with severe reperfusion injury, a false sense of victory can occur and deterioration of the cat can be missed unless vigilance continues. This is especially true for decompensation of the heart and the acute development of pulmonary edema. During this time additional medications that are given orally for the heart can be started and these include ACE inhibitors, aspirin, and potentially clopidogrel. If the cat begins to eat at this time, it is a good prognostic indicator.

Long-term management. The problems to address in the long-term include treating the (1) underlying cardiac disease and managing congestive heart failure if present, (2) preventing reembolization, and (3) providing the needed care and management for recovery of the limbs form the thromboembolic event.

There remains controversy as to the correct treatment of cats with hypertrophic and restrictive cardiomyopathy. In general, cats that have had an episode of pulmonary edema are treated with angiotensin-converting-enzyme inhibitors, furosemide at a dose that prevents pulmonary edema and yet preserves renal perfusion. In cats that have not had an episode of pulmonary edema the use of beta-adrenergic blockers or calcium channel blockers is unclear. Given that the majority of cats that leave the hospital after thromboembolism die of congestive heart failure determination of the best treatment of the underlying heart disease is a paramount goal.

It is clear that these cats need treatment to prevent reembolization which occurs at the rate of about 25% as reported in the most recent reports, but what is uncertain is how this is accomplished. For many decades some have suggested the use of aspirin, while others say it does no good. Studies in the early 1970’s showed that experimentally cats treated with aspirin, if thromboembolism did occur had less severe clinical signs and recovered quicker. But still, thromboembolism occurs. In humans aspirin alone is frequently inadequate to control thromboembolism, whereas, anticoagulation treatment decreases the recurrence. However, treatment with anticoagulants such as coumadin requires rigorous monitoring that is rarely possible in cats. The LMWH could be an alternative, although when these have been used thromboembolism still developed and the target levels were never obtained at the dose used and the half-life appears short. The latter is problematic because the drug must be administered parenterally and it appears that twice daily administration is inadequate. This type of treatment is likely not practical. Recently, an alternative treatment has been suggested which is antiplatelet rather than anticoagulation. This involves the combination of aspirin with another drug that works by a different mechanism to inhibit platelet aggregation. This drug is clopidogrel (Plavex) and recent studies have shown this to be a safe drug in cats.

The mediators of platelet activation include thrombin, ADP, collagen, and thromboxane A_2. Thrombin stimulates platelets to release ADP and thromboxane A_2. Collagen activates platelets to recruit other platelets. The antithrombotic effect of aspirin occurs by irreversibly acetylating cyclo-oxygenase to block formation of thromboxane, but it has no effect on platelet activation by thrombin and ADP. Clopidogrel which is a thienopyridine ADP receptor antagonist exerts its effect of inhibiting platelet aggregation through irreversible inhibition of ADP receptors on the platelet membrane blocks and indirectly reduces binding of fibrinogen and von Willebrand factor. It is the active metabolite (produced through hepatic metabolism) that is the active form of the drug. Clopidogrel also inhibits glycoprotein IIb/IIIa receptor complex and reduces serotonin release from platelets. Recent studies have shown clopidogrel to be safe in cats, although efficacy has not been shown. Also, the lowest dose studied may still be too high (18.75 mg once daily). We are currently using a dose of 7 mg once daily in conjunction with 40 to 81 mg of aspirin every three days. This treatment has not been proven to be effective. We routinely place cats on aspirin when left atrial enlargement is present and a combination of aspirin and clopidogrel if the cat has suffered from thromboembolism.

Physical therapy and protection of the embolized limb is required in cats. When cats have recovered from the dangers of the immediate thromboembolism there is still a protracted recovery of limb function. This time depends on the severity and length of the ischemia. Cats that are presented with paralysis of the hindlimbs, but with good upper thigh motion, tail function and pad color that reveals some perfusion of the hindlimbs, weak to no upper thigh motion, no tail motion and pad color that indicates little perfusion can take months to recover. Severe ischemia experimentally induced in the limbs of cats reveals that nerves with transfascicular infarction have prolonged regeneration and sometimes it is never complete (studied as long as 16 months post-insult). In the regenerating nerve of cats the number of large myelinated fibers is reduced and replaced by large numbers of small size myelinated fibers. This phenomenon is due to extensive branching of regenerating nerve fibers that never reach their target because of the concurrent loss of muscle tissue. Also contributory is the damage to not only the axons but the Schwann cell basement membranes, vessels and endoneurial components. These factors disturb the regeneration of nerves that have no guidance. Finally, endoneurial fibrosis may occur and prevent further regeneration. In general, if demyelination has occurred with surviving Schwann cells recovery can happen in a short time (days to weeks), but if the peripheral
nerve is to regenerate the rate of growth is 1 to 4 mm/day (and this assumes that factors to hinder this growth do not develop (fibrosis).

Only time will tell which cats will regenerate enough nerve with adequate muscle mass to restore ambulatory function. The amazing fact is, many cats can do this. Disappointingly, before the time has elapsed for these regenerative processes some cats may actually survive the ischemia and reperfusion only to have a leg that never recovers adequate perfusion for regeneration. Such a situation results in euthanasia or amputation of the limb. Some cats may require perfusion studies to determine the status that guides treatment. During the recovery of the limbs the act of dragging the limbs and the sensation return can cause problems. Necrosis, infection and self-mutilation can occur and undermine the success of saving the cat from the critical insult. Bandaging to protect the lower leg from abrasion when the cat drags its legs must be done with care because of the reduced circulation. If skin erosions develop aggressive treatment with cleansing, silver sulfadiazene ointment, and bandaging protection are required. The most common infection of such sores is Pseudomonas, similar to burn injuries. Immediate attention is required if a fever develops and an elevation in the white blood cell count. When this type of lesion develops the limb may not be salvaged and amputation is required. Although this is a desperate measure, it is surprising how cats can survive the surgery and live with the single hindlimb.

In summary, the treatment of thromboembolism in the cat entails multitasking to treat the cardiac disease, emergency situation and long-term management. An understanding of the pathophysiology will guide us in designing studies to answer the clinical questions. We have made progress in the treatment of this disease, but there is still a long way to go. The fortunate situation is that there are cats that can survive despite our limited knowledge.