Thromboembolic disease in dogs and cats

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Louise gained her Diploma in Advanced Veterinary Nursing (Surgical) in 2004, followed by her Diploma in Advanced Veterinary Nursing (Medical) in 2007, Veterinary Technician Specialist (Emergency and Critical Care) in 2011 and Veterinary Technician Specialist (Anaesthesia) in 2014, making her a member of both AVECCT and AVTA. She has contributed to over 25 journal articles and book chapters, and lectures regularly on all aspects of anaesthesia, emergency and critical care and infection control. She has worked as Head Nurse for PetMedics in Manchester, the largest emergency clinic in the UK, for the past 13 years, and is now Clinical Director.

Louise's interests include all aspects of emergency care but particularly trauma, as well as anaesthesia, infection control and wound management. Louise is the co-author of Practical Emergency and Critical Care Veterinary Nursing as well as Wound Management in Small Animals: A Practical Guide for Veterinary Nurses and Technicians, the BSAVA Pocketbook for Nurses and the forthcoming A Veterinary Nurse's Guide to Infection Prevention and Control, due 2015.

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Introduction

Thromboembolic disease in dogs and cats is relatively rare compared to the incidence in people. Deep venous thrombosis and subsequent embolic episodes are not uncommon occurrences in people yet are not seen in our small animal patients. The thromboembolic disease that we see in veterinary patients is usually secondary to another disease, which results in a **hypercoagulable** state.

In dogs, Cushing's disease, glomerulonephritis or other protein-losing nephropathies, sepsis or neoplasia can predispose the patient to thromboembolic episodes.

Heart disease is the most common cause of thromboembolic disease in cats. Feline aortic thromboembolic disease (ATE) is a serious and life-threatening sequel to cardiomyopathy in cats. Less common causes include neoplasia (especially pulmonary neoplasia), glomerulonephritis, inflammatory bowel disease, sepsis and other coagulopathies. Although cardiomyopathy is the most common cause, the pathophysiologic mechanisms leading to the condition are not clearly understood.

Physiology

Thrombosis, or the formation of matrices of platelets, fibrin and cellular debris, occurs within the intravascular space. This can lead to thromboembolism due to three factors (described by **Virchow's triad**): hypercoagulability, blood stasis and endothelial cell injury. The presence of two of the three factors significantly increases the chances of thrombosis. Thrombosis is known to occur in various diseases, including immune-mediated diseases, neoplasia, infectious diseases and inflammatory diseases (pancreatitis, sepsis).

Hypercoagulability

Hypercoagulability can result from platelet hyper-reactivity, excessive coagulation-factor activation, natural anticoagulant deficiency, hypofibrinolysis or a combination of any of these causes. Platelet hyper-reactivity can result from increases in platelet activators. This includes direct stimulation by inflammatory cytokines, release of other platelet agonists and hypoalbuminaemia-mediated increase in thromboxane A2 (a prothrombotic).

Endothelial cell damage, leading to decreased availability of platelet inhibitors (prostacyclin, nitrous oxide and ADPase), or administration of antiplatelet drugs can lead to a reduced coagulation inhibition (Yagi, 2014).

Coagulation factor

Excessive coagulation factor activation occurs when increased expression of tissue factor (TF) by endothelial cells, macrophages and cell-derived micro-particles is induced by endotoxins or inflammatory mediators. An increased exposure of already existing TF can also occur due to endothelial cell damage.

Anticoagulant deficiency

Deficiencies in natural anticoagulants may be genetic or acquired in origin:

- *Antithrombin (AT)* deficiencies can arise from hepatic failure, protein-losing nephropathies, consumption due to a pathologic increase in thrombin (DIC or massive thromboembolism) or suppression from drugs (Liss, 2010). Protein C deficiencies can develop due to sepsis, malignancy, pancreatitis, DIC and hepatic or cardiac failure.
- *Tissue factor pathway inhibitor* (TFPI), which inhibits coagulation, can be deficient in animals with

hypercholesterolaemia, thus making hypercholesterolaemia a risk factor for thromboembolism (Liss, 2010).

- *Hypofibrinolysis* has not been very well defined in veterinary medicine, but is thought to occur with an increased level of plasminogen activator inhibitor (PAI-1) and/or α2-antiplasmin (Yagi, 2014).
- *Hypoplasminogenaemia* has been reported in traumatised dogs and horses with strangulating obstructions.

Impaired blood flow

Areas of *impaired blood flow* can lead to varying degrees of blood stasis. Changes in cardiovascular anatomy and cardiovascular function can cause abnormal or reduced flow, these being risk factors for thrombosis. Left atrial dilatation, causing an aberrant blood flow, is a well documented cause of Feline ATE. Other conditions associated with altered blood flow include hypovolaemia, hyperviscosity disorders, neoplasia, vascular and cardiac abnormalities.

Clinical manifestations of thrombosis

When the balance of haemostatic forces is tilted towards thrombosis, a hypercoagulable state exists causing thromboembolism and manifesting clinically as its consequences.

In canine patients, thromboembolism is seen most commonly with protein-losing nephropathy, neoplasia, immune-mediated haemolytic anaemia (IMHA), necrotising pancreatitis, hyperadrenocorticism and corticosteroid therapy. Having multiple predisposing conditions increases the likelihood of thromboembolism.

Common manifestations in dogs involve arterial and venous thromboembolism with involvement of multiple organs. Single-organ manifestations include arterial thromboembolism in dogs with atherosclerosis, and pulmonary thromboembolism in dogs with IMHA.

Occurrence of thromboembolism in cats seems to be more rare, but manifests similarly to the condition in dogs. Whilst venous thromboembolism may occur in cats with neoplasia, cardiac disease and multisystemic diseases, aortic thromboembolism associated with cardiomyopathy is the most common manifestation in this species.

Typically, due to hypertrophic cardiomyopathy, a thrombus (or thombi) forming in the left ventricle leads to an embolus at the aortic trifurcation, causing what is known as a 'saddle thrombus'. Less commonly, an embolus forms proximal to the renal artery or brachial vessel. This leads to vasoconstriction in the vessels occluded by the embolus, leading to further reduced collateral flow and ischaemia.

Pulmonary thromboembolism

Pulmonary thromboembolism (PTE), or the lodging of a thrombus in the pulmonary arterial vasculature leading to the capillary beds in the blood gas barrier, causes dead-space ventilation (alveoli that are ventilated but not receiving perfusion). Common clinical situations where PTE may occur involve diseases leading to a hypercoagulable state. The clinical signs of PTE include the sudden onset of dyspnoea and compensatory signs of hypoxaemia and subsequent hypoxia.

Depending on the proportion of the lung affected by the thrombus, there may or may not be clinical signs. In a retrospective study, only 38% of dogs and 14% of cats with PTE documented at necropsy were suspected of PTE during treatment, and 41% of dogs and 44% of cats were clinically silent (Johnson, Lappin, & Baker, 1999; Norris, Griffey, & Samii, 1999; LaRue & Murtagh, 1990). In retrospective studies the diseases most commonly associated with PTE in dogs were cardiac disease, neoplasia and sepsis, whilst in cats, cardiac disease and neoplasia were identified, (Johnson *et al.,* 1999; Norris *et al.*, 1999; LaRue & Murtagh, 1990).

Aortic thromboembolism

Aortic thromboembolism (ATE) commonly manifests as a saddle thrombus, which is the lodging of a thrombus at the trifurcation of the distal aorta into the iliac arteries, although emboli can occur in different locations throughout the body. Saddle thrombi can affect both cats and dogs, but typically arise from differing aetiologies.

Feline ATE

Feline ATE is commonly caused by cardiac disease, has an acute onset, and results in hind-limb paresis. Feline ATE most commonly affects middle-aged cats, with a male:female ratio of 2.5:1 (Moore, Morris, & Dhupa, 2000; Laste & Harper, 1995; Schoeman, 1999), this is due primarily to the greater predisposition of male cats that develop hypertrophic cardiomyopathy (HCM) (Moore *et al.*, 2000). 12-17% of cats with HCM experience thromboembolism, though the location may not always be the iliac vessel (brachial, mesenteric, renal and/or cerebral vasculature have been documented).

Feline ATE does not necessarily arise from HCM, with dilated, intermediate and restrictive cardiomyopathies being other possibilities. Approximately half of cats with ATE displayed some form of congestive heart disease, and 70-80% of cats with left sided disease displayed ATE as the first manifestation of the disease, as noted in two retrospective studies (Moore *et al.,* 2000; Laste & Harper, 1995; Schoeman, 1999). Left atrial wall enlargement increases the risk of thromboembolism because blood flow is altered and could become stagnant, as well as endothelial injury causing increased platelet activation and triggering of coagulation. Hyperthyroidism and neoplastic disease (especially pulmonary neoplasia) are also associated with Feline ATE.

Most patients present with acute onset of lameness, paresis, or paralysis of the affected limbs. Affected limbs are nearly always painful, musculature is frequently firm and pulses are weak or non-palpable. Nail beds and pads may appear pale to cyanotic (**Figure 1**), and the limb may feel cool. In one study, some motor ability was present in 34% of cases. Forelimb- and unilateral hind-limb episodes were more likely to have motor function present (Moore *et al.,* 2000).

The prognosis associated with Feline ATE is generally considered to be poor. Retrospective studies documented survival rates to discharge as between 33% and 39% (Kramer, 2003). These reports however, may overestimate the negative prognosis. Kramer reports that cats with ATE may not be given enough time to re-establish collateral circulation and are often euthanized too early in the course of treatment. In his experience,

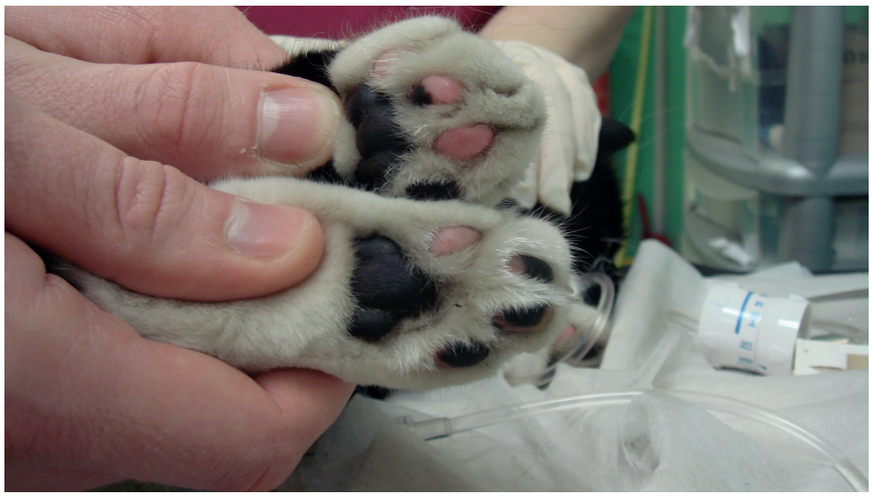

Figure 1. Paler footpads noted in a feline patient with suspicion of ATE

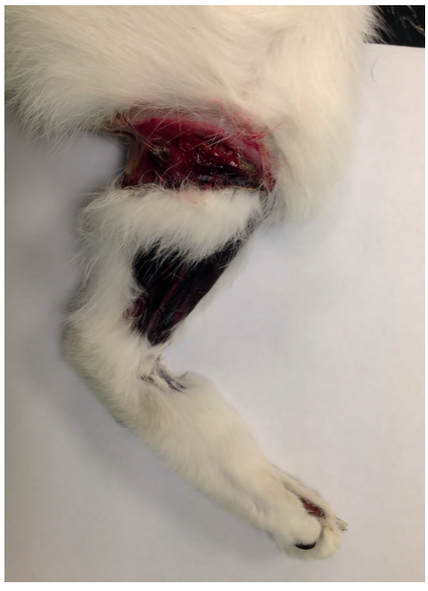

Figure 2. Distal necrosis present in the affected limb of a feline patient with ATE

between 50-75% of cats presenting with ATE are discharged, including those that develop varying degrees of distal necrosis of an affected limb (**Figure 2**). Cats with single-limb involvement have a better prognosis than those with multiple-limb involvement (80% discharge rate reported).

Negative prognostic indicators that may support the decision for early euthanasia include: the presence of a large ball thrombus in the left atrium or left ventricle, the presence of an atonic urinary bladder and markedly decreased anal-sphincter tone, hyperkalaemia, azotaemia and/or hypothermia at the time of presentation or evidence of renal or mesenteric artery involvement.

Kramer (2003) reported significant incidence of recurrence of an episode of Feline ATE of between 37% and 50% in cats that did recover to discharge. There appeared to be no significant difference between cats that were being treated with aspirin or those treated with warfarin. The median survival time of discharged cats has been reported to be 9-10 months.

Canine ATE

Aortic thromboembolism in dogs is not strongly skewed towards cardiac disease as it is in cats, though it remains an underlying cause. Other associated conditions include sepsis, hyperadrenocorticism, neoplasia and protein-losing disease.

ATE can occur in two ways in dogs, with approximately a third of the cases arising due to thrombi travelling downstream to lodge in a narrower part of the vasculature. In the remaining two thirds, the thrombus is thought to form at the location of the embolus. Peracute presentation of hind-limb paralysis, is less commonly seen; a majority of dogs suffering ATE demonstrate pain, lameness, weakness and paresis/paralysis chronically over 2-6 months.

An abundance of collateral circulation allows dogs to tolerate complete obstruction of a blood vessel, better than cats, though pain can be induced with exercise due to lactic acid accumulation from the inability for reduced perfusion to keep up with demands (Van Winkle, Hackner, & Liu, 1993).

Cerebrovascular disease

Cerebral infarction due to thromboembolism and hypoperfusion results in reduced cerebral perfusion, causing ischaemic brain injury. Veterinary evidence for cerebrovascular disease is lacking, but human medicine points towards a lack of hypercoagulable state in patients with cerebral infarction. Cerebral blood flow can be affected by all factors of Virchow's triad (hypercoagulability from loss of anticoagulation, endothelial inflammation and blood stasis due to bi-directional cerebral blood flow), potentially resulting in the thromboembolism (Yagi, 2014).

Treatment

Treatment of these clinical states is mainly symptomatic:

- Pain should be controlled, ideally by pure opioids, e.g. methadone.
- Hypoxemia should be treated with oxygen supplementation, either in the form of nasal O2 cannulas or an oxygen cage.
- Anti-platelet therapy should be instituted:
  - *aspirin* prevents platelet aggregation by inhibiting thromboxane A2
  - *clopidogrel* (Plavix) is a newer anti-platelet drug, also used to prevent aggregation of platelets
- Anti-coagulant drugs
  - heparin inactivates Factors IX, X, XI, and XII; it can cause bleeding and should be used with caution (Liss, 2010); recommendations are to treat until the activated partial thromboplastin time (aPTT) is prolonged by 1.2-2.5 times; it can also cause heparin-induced thrombocytopenia
  - low-molecular-weight heparin (LMWH) has a longer half-life than heparin and won't cause bleeding or prolongation of the aPTT because it preferentially inhibits Factor X only. It is usually expensive
- Fibrinolytic agents (streptokinase, t-PA) are highly controversial and come with very severe side effects. By destroying clots, they cause massive reperfusion-ischemia injury, which can be life threatening. These drugs activate plasminogen to convert to

plasmin, thereby dissolving fibrin clots (Smith, 2009).

Conclusion

Knowing which diseases increase risk and how they affect the Virchow triad can aid in early diagnosis and direction of treatment, as patient survival is very dependant on rapid diagnosis and the institution of appropriate therapy without delays.

Excellent nursing care is paramount when dealing with these patients. All risk factors for further thromboemboli should be taken into consideration (e.g. catheters, venipuncture sites, recumbency), while nursing interventions such as reduction of venous stasis, e.g. passive range of motion exercises, standing exercises, limb massage and regular turning of recumbent patients, are also important.

Despite the difficulties in treating these cases, and what is generally considered to be a low outcome in success rates of treatment, they are hugely rewarding cases to nurse.

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