# Feline Aortic Thromboembolism

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## ABSTRACT

Aortic thromboembolism is one of the most serious and difficult-to-manage complications of feline cardiac disease. Most, but not all, cats presenting with signs of aortic thromboembolism are found to have underlying cardiac disease at the time of presentation. In most cases no underlying disease has been diagnosed prior to presentation with paresis/paralysis and profound anxiety. This article will review commonly used treatments for thromboembolism and agents proposed for prophylaxis. Many of the proposed treatments are themselves associated with a high morbidity rate and long term clinical trials are required to make comparative risk-to-benefit ratio assessments of these different options. In cats which do survive the initial treatment, clinicians are still faced with the perplexing problem of long term thrombus prevention, as a majority of cats have been shown to re-embolise despite prophylaxis.
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## INTRODUCTION

Feline aortic thromboembolism (FATE) is a common and serious complication of feline cardiac disease associated with a high morbidity and mortality (Liu *et al* 1981, Flanders 1986, Harpster 1986, Van Vleet & Ferrans 1986, Pion 1988, Slappendel 1988; Atkins *et al* 1992, Laste & Harpster 1995, Behrend *et al* 1996, Fox 1999; 2000, Rodriguez & Harpster 2002). Thrombi are believed to form within the left atrium (LA)/auricle or, less frequently, the left ventricle (LV) or right side of the heart (Harpster & Baty 1995, Laste & Harpster 1995; Rush *et al* 1998, Fox 1999; 2000, Rodriguez & Harpster 2002). Thromboembolisation (TE) is believed to occur when an embolus breaks free from a thrombus and enters the systemic arterial circulation. The consequences of this depend upon the site of embolisation, the completeness of the resultant obstruction, the patency of the collateral circulation and the duration of the obstruction. It is widely reported and accepted that, in cats, greater than 90% of emboli lodge at the distal aortic trifurcation ("saddle thrombus").

More than 90% of reported cases of aortic TE are in cats with underlying cardiac disease (Kittleson 1998). Occasionally affected cats have no evidence of cardiac disease or other underlying aetiology and no cause can be identified (Sisson & Thomas 1995, Baty 2001). All forms of cardiomyopathy are acknowledged risk factors, however there is currently no reliable method of determining which affected cats are most at risk of developing TE disease. Echocardiographically, the presence of LA enlargement, spontaneous echo contrast (smoke) in the LA and/or the presence of intra-cardiac thrombi are recognised risk factors. However, at the time of clinical presentation with aortic TE, a majority of cats have no previously diagnosed cardiovascular disease (Killingsworth *et al* 1986, Laste & Harpster 1995, Schoeman 1999).

## PATHOGENESIS

The suspected pathogenesis of thrombus formation within the heart requires the presence of one or more of three essential conditions, known as Virchow's triad, to be present. These are local vessel (or tissue) injuries, circulatory abnormalities and altered blood coaguability (Helenski & Ross 1987, Pion & Kittleson 1989, Sisson & Thomas 1995, Rush *et al* 1998, Fox 1999; 2000, Rodriguez & Harpster 2002). These thrombotic factors are invariably present to some degree with cardiac disease. For example LA enlargement results in stretching of the endocardium which can microscopically alter the endothelium, exposing endocardial collagen, a potent inducer of platelet aggregation and an activator of the extrinsic clotting

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cascade, potentially initiating thrombosis (Liu *et al* 1993, Behrend *et al* 1996, Rush *et al* 1998, Fox 1999; 2000, Rodriguez & Harpster 2002). Activated platelets release adenosine diphosphate (ADP), serotonin and thromboxane A2 (TXA2) which promote further platelet aggregation and vasoconstriction. The final product of the coagulation cascade, fibrin, polymerises within the platelet aggregate forming an organised thrombus that adheres to the vascular wall. Sluggish blood flow, associated with factors such as LA enlargement and mitral regurgitation, enable activated clotting factors to accumulate, thus increasing the risk of thrombosis, while factors that increase blood turbulence (enlarged papillary muscles, mitral regurgitation, fibrotic intra-ventricular lesions) can enhance platelet activation and aggregation (Laste & Harpster 1995, Behrend *et al* 1996, Rodriguez & Harpster 2002). Increased blood coaguability (i.e. increased coaguability and/or reduced lysis potential) may also be an important contributing cause of thrombosis in cats. Compared to other domestic species cats appear to have inherently higher platelet reactivity and have platelets which are larger (Weiser & Kociba 1984, Thompson *et al* 2001), with greater storage capacity (Sisson & Thomas 1995). Feline platelets have also been demonstrated to be extremely sensitive to serotonin-induced aggregation (Flanders 1986, Harpster 1986, Pion & Kittleson 1989, Sisson & Thomas 1995). In addition, compared to healthy cats, some cats with cardiomyopathy have been shown to have platelets which are extremely reactive to ADP (Helenski & Ross 1987, Harpster & Baty 1995, Sisson & Thomas 1995, Rodriguez & Harpster 2002) and this reactiveness may be an additional predisposing factor to TE. Consequently, cats are potentially in a constant state of increased coaguability which may explain the more frequent occurance of TE disease in cats (Behrend *et al* 1996). Blood stasis, adjacent to and beyond an occluding embolus, probably also contributes to clot elongation, intravascular coagulation and delayed lysis.

Since FATE was first described in the veterinary literature much has been learnt about its patho-physiology. Experimental studies have demonstrated that physical occlusion of the terminal aorta alone will not reproduce the clinical syndrome. This is due to the presence of collateral blood flow through spinal and epaxial arteries which maintains adequate circulation. However, in the presence of a thrombus, this collateral circulation is inhibited and the clinical syndrome (FATE) reproduced (Butler 1971). This led to the hypothesis that vasoactive substance(s), released from the thrombus, result in inhibition of the collateral circulation. Further experimental work demonstrated that the clinical syndrome can be induced by injection of serotonin between two ligatures in the terminal aorta and that administration of serotonin antagonists, prior to experimental thrombosis, will prevent this loss of collateral circulation (Butler 1971, Olmstead & Butler 1977). This has led to speculation that vasoactive compound(s), e.g. serotonin released from the blood clot, may be the causative agent(s) in this clinical syndrome.

## CLINICAL PRESENTATION AND DIAGNOSIS

Arterial TE can result in a diverse range of clinical signs depending upon which systemic arterial bed is embolised. In cases of aortic TE, affected cats generally have a peracute presentation with lateralising posterior paresis or paralysis, often with concurrent signs of congestive heart failure (CHF) and apparent pain and anxiousness. A majority of cats have no previously diagnosed cardiovascular disease (Schaub *et al* 1982, Laste & Harpster 1995). In two retrospective studies of aortic TE only 11% and 23% of cats, respectively, had previously diagnosed cardiac disease (Laste & Harpster 1995, Schoeman 1999). Aortic occlusion can be complete or partial in nature, resulting in a varying degree of clinical signs. In the case of complete obstruction, blood flow to the hind legs is prevented while in partial obstructions, some blood flow around the occluding embolus is maintained. In partial obstructions weak femoral arterial pulses may be palpated. Hind limb signs may be unilateral and/or unequal, muscles may not become firm and some motor function may be maintained.

In cases of complete aortic TE, the distal limbs and pads are cold and cyanotic or pale. Hind limb nail beds are cyanotic and do not bleed when cut back to expose the vascular ungual process. Femoral arterial pulses are generally absent but this is not pathognomonic for FATE as they can be difficult to palpate, especially in uncooperative or obese patients or those in pain. The cranial tibial and gastrocnemius muscles are often firm and painful or become so, 10 to 12 hours after embolisation due to ischaemic myopathy. In most cases they then become softer 24 to 72 hours later. The extreme anxiety initially experienced by most affected cats generally subsides with time.

Loss of motor function to the caudal body is variable. Some cats lose the ability to move their limb(s) starting at the hip, whereas others only lose the ability to move the limb(s) distal to the stifle or the hock. These latter cats can extend and flex their hips so "walk" on their stifles in a dragging manner but are unable to flex or extend their hocks. Many cats retain the ability to move their tail and retain anal tone and the anal reflex. Bladder function is often normal although urine retention may occur. The distal limbs are usually swollen, with little spontaneous movement; sensation from the lower leg is poor and reflexes are absent.

Most cats present with concurrent signs of CHF or cardiac disease. Thoracic auscultation may reveal systolic heart murmurs, gallop rhythms, arrhythmias, pulmonary crackles or muffled heart and/or lung sounds. Cats are generally tachypnoeic or dyspnoeic. Most are clinically dehydrated and hypothermic at the time of presentation. A majority of affected cats will vocalise extensively, presumably as a result of the profound pain, distress and anxiety they are experiencing.

A diagnosis of FATE can usually be made based upon presenting clinical signs and on the results of physical examination. Initial diagnostic efforts should be directed towards defining the site and severity of vascular obstruction and identifying the nature and severity of any underlying cardiac disease. Risks to the patient must be assessed. It is often necessary to initiate therapy for CHF and stabilise the patient (rehydration, reduce

hypoxaemia, establish electrolyte balance, etc) prior to attempting invasive or stressful diagnostic procedures.

## NATURAL HISTORY AND PROGNOSIS

The prognosis should be considered guarded in cases of complete aortic occlusion. The short term prognosis depends upon the nature and responsiveness of any underlying cardiac disorder, the heart failure status of the patient and the severity of the rhabdomyolysis occurring secondary to ischaemic myopathy. Acute development of hyperkalemia may result from sudden tissue reperfusion and confers a grave prognosis. Embolisation represents a significant clinical setback as cats with cardiomyopathy but with no signs of FATE have a better probability for long term functional survival.

In cats with distal aortic TE that receive no definitive therapy, the outcome depends upon the extent of the occlusion and the time to reperfusion, either via the primary vessel or the collateral circulation. About 50% of cases will regain all or most hind limb motor function within one to six weeks (Kittleson 1998). The return to function in this situation is due to the activity of the cat's fibrinolytic system. The degree and rapidity of thrombus dissolution depends upon the activity of an individual cat's fibrinolytic system, the original extent of the TE and any existing thrombosis/lysis imbalance.

Following resolution of blood flow, whether spontaneously or as the result of therapeutic intervention, motor ability may begin to return in one or both legs within 10 to 14 days. By three weeks significant motor function has often returned and it is typically better in one leg than the other. Motor function may be completely normal by four to six weeks post embolisation although a conscious proprioceptive deficit or conformational abnormality (e.g. extreme hock flexion) may persist as a result of residual peripheral ischaemic neuropathy and secondary muscle contracture.

In two recent retrospective studies of FATE, involving 100 and 49 TE events respectively (Laste & Harpster 1995, Schoeman 1999), survival rates of 37% and 39% were reported. However 35% and 33% of cats in each report were euthanased during the initial TE episode due to the poor prognosis offered. Hence, potential survival rates may in fact be higher than reported. Unfortunately, most cats experience additional TE episodes, within days to months of the initial event, although survival for several years with repeat embolic events has been reported (Fox 1999; 2000). Average reported long term survival rates were 11.5 months and 13.4 months respectively (Laste & Harpster 1995, Schoeman 1999).

## TREATMENT AND PROPHYLAXIS (*Table*)

Controlled, prospective clinical trials comparing therapeutic and prophylactic protocols are lacking in the veterinary literature. There are various medical treatments used for acute and long term management of emboli however their real efficacy is unsubstantiated. If an embolus is successfully removed, clinicians are still faced with the perplexing problem of long term thrombus management. Treatment for FATE is aimed at preventing further thrombus formation, promoting circulation to ischaemic tissues, managing pain and dissolving the existing thrombus, as well as treating the underlying cause(s). It has been reported that if a patient's primary heart disease does not cause death, the peripheral disturbance to the circulation will, in time, be overcome (Holzworth *et al* 1955, Bonagura 1994, Schoeman 1999). In this review reported therapies for FATE will be discussed, however it must be stressed that the patient's general and cardiovascular status must be stabilised.

### (1) General Supportive Therapy

Supportive therapy is critical to the management of FATE and is generally instituted first in an effort to stabilise the patient. It is important to maintain electrolyte balance and in particular hydration, as most cats are clinically dehydrated at the time of presentation. However, intravenous fluid therapy should be instituted judiciously to avoid exacerbating any existing pulmonary oedema. As a majority of presenting cats are also hypothermic, heating pads, hot water bottles and appropriate bedding should be used to aid in the elevation of body temperature. Providing warmth to the hind limbs also encourages vasodilation potentially improving blood flow to ischaemic areas. Nasal oxygen should be provided in cases with underlying CHF and tachypnoea or dyspnoea. Nutritional support is also of primary importance and placement of a nasooesophageal feeding tube is advocated for anorectic cats.

Physiotherapy is an important adjunct therapy to encourage movement of non-functional muscles, reduce muscle wastage and attempt to improve blood flow. Self-mutilation is common following aortic TE and is evidenced by licking or chewing of the toes or lateral hocks, devitalised as a result of ischaemia. This can usually be controlled by the application of loose fitting bandages, stockinettes or some other barrier. Affected cats should be confined to a cage with soft bedding to prevent further injury.

### (2) Analgesic Therapy

Affected cats display signs of profound pain and anxiety so some form of analgesic therapy is appropriate. Aspirin is usually administered at a dose of 25mg/kg, every 48 to 72 hours, to help prevent platelet aggregation and also to potentially reduce myalgia, associated with ischaemic myopathy. However, it will not control the severe pain associated with TE (Olmstead & Butler 1977, Fox 2000). Opioids offer good analgesia with minimal effects on myocardial contractility, preload and afterload (Rodriguez & Harpster 2002) and are generally required for at least 24 to 36 hours after embolisation. Oxymorphine can be administered (0.05 to 0.15mg/kg) for moderate to severe pain (Killingsworth *et al* 1986, Kittleson 1998, Rodriguez & Harpster 2002) and butorphanol (0.2 to 0.4mg/kg) for mild to moderate pain (Killingsworth *et al* 1986, Rodriguez & Harpster 2002). These drugs can be administered intravenously, intramuscularly or subcutaneously every four hours as needed. Lumbosacral epidural analgesia may also be of use in pain management in cats with distal aortic TE.

### (3) Surgical Embolectomy

This has met with mixed results. It is generally associated with a high mortality rate both from anaesthetic/surgical complications (decompensated CHF, disseminated intravascular coagulation,

hypothermia, arrhythmias) and from reperfusion injury, due to rapid re-establishment of circulation and washout of potassium and other metabolites from ischaemic tissues. In addition, by the time a patient has been sufficiently stabilised, significant neuromuscular ischaemic injury has probably occurred. If surgery is to be considered it should therefore be performed within 12 hours of embolisation (Pion & Kittleson 1989, Sisson & Thomas 1995, Fox 2000). Kittleson (1998) has proposed that surgery may be a viable option (in a patient that does not have severe CHF) if two things could occur; the legs could be "flushed" with sterile saline prior to allowing reperfusion (saline infused into the arterial tree and the blood/saline wash removed via cannulas in the femoral veins) and treatment with insulin/glucose or calcium could be instituted, immediately upon reperfusion to combat potential hyperkalemia. These techniques have not been trialed, either clinically or experimentally, and it is generally accepted that surgery should be avoided.

**(4) Catheter Embolectomy**

Removal of emboli has been attempted using balloon catheters however this procedure is difficult, generally unsuccessful in cats and is associated with the risks of anaesthesia, acute reperfusion injury (Pion & Kittleson 1989) as well as any subsequent TE at the catheter site.

**(5) Vasodilator Agents**

Vasodilator therapy has been advocated to promote collateral circulation. Various agents have been proposed; hydralazine and acepromazine maleate are the most commonly used. In addition to its vasodilatory properties, acepromazine maleate possesses sedative properties which may offer some benefit in these very anxious patients. However these agents have the potential to exacerbate pre-existing hypotension and hypothermia. Experimentally, they have not been shown to alter platelet-induced obstruction of collateral blood flow caused by vasoactive chemicals such as serotonin (Fox 1999; 2000).

**(6) Thrombolytic Therapy**

Thrombolytic therapy has been associated with high morbidity and mortality in limited clinical trials (Pion & Kittleson 1989, Fox 2000). Thrombolytic drugs have the ability to dissolve an existing thrombus and TE within blood vessels. All require an adequate circulatory concentration of the proenzyme plasminogen which is converted to plasmin to induce lysis. Ideally thrombolytic therapy should be initiated within four hours of clinical signs to maximise clot dissolution and reperfusion (Rush *et al* 1998, Rodriguez & Harpster 2002). However as outlined above reperfusion syndrome is a major complication of these techniques.

**i. Streptokinase and Urokinase**

Both of these agents possess little specific affinity for fibrin; they activate both the circulating and bound plasminogen, converting it to plasmin in a relatively indiscriminate manner. Plasmin, formed in the circulating blood, is initially rapidly neutralised by alpha-2-antiplasmin but when this is saturated the circulating concentration of plasmin suddenly rises. Plasmin degrades numerous circulating proteins including fibrinogen, coagulation factors, plasminogen and the administered activator itself (Pion 1988, Pion & Kittleson 1989). Degradation of circulating fibrinogen results in elevated levels of fibrinogen degradation products (FDPs) which are, in themselves, potent anticoagulants (Pion 1988, Pion & Kittleson 1989). In cats with thrombi this leads to dissolution of the thrombus with restoration of perfusion to affected tissues. However reperfusion syndrome (hyperkalemia and metabolic acidosis) is a major complication of this rapid dissolution. Additionally, the activation of circulating plasminogen, production of FDPs and degradation of coagulation factors predispose the patient to haemorrhage (Killingsworth *et al* 1986, Pion & Kittleson 1989, Ramsey *et al* 1996, Fox 1999; 2000, Thompson *et al* 2001).

A controlled, large scale clinical evaluation of streptokinase in naturally occurring FATE and cardiomyopathy has not been reported (Fox 1999). Clinically it has been used sporadically with inconsistent results. Killingsworth *et al* (1986) administered strepotokinase to cats with experimentally induced TE. A loading dose of 90,000IU was given intravenously over 20 to 30 minutes followed by a constant rate infusion of 45,000IU over a three hour period. While no adverse effects were reported, there was no significant improvement as measured by angiograms and thermal circulatory indices or any statistically significant reduction in mean thrombus weight. In this study thrombi were isolated from the systemic vascular system in a sac between two ligatures so the therapeutic potential was probably underestimated (Killingsworth *et al* 1986, Pion & Kittleson 1989). In addition, Kittleson (1998) does not believe that the drug was administered for long enough to be effective at this dose.

Similarly, disappointing results have been reported with streptokinase administration to a group of eight cats with naturally occurring distal aortic TE or LA thrombosis secondary to myocardial disease (Ramsey *et al* 1996). These cats received a loading dose of 90,000IU streptokinase over 30 minutes followed by a maintenance dosage of 45,000IU/hour for variable periods. All patients died suddenly during the maintenance infusion. The cause of death was not identified in most cases. In a retrospective study of streptokinase administration in 46 cats with aortic TE, receiving varying doses of streptokinase, only 33% of cats were discharged from hospital following treatment (Moore *et al* 2000). There was found to be no difference in survival based on the total dose of streptokinase, on dosage on a IU/kg basis or on the duration of the infusion.

In people the local intra-arterial administration of these agents provides effective thrombolysis at doses below those usually associated with systemic fibrinolysis (Pion & Kittleson 1989). In cats with aortic TE, it is feasible that the aorta could be catheterised via the carotid artery and the catheter advanced to be proximal to the occluding thrombus. Anaesthesia could include the use of ketamine and diazepam, in conjunction with local anaesthesia (Pion & Kittleson 1989).

Another approach to thrombolytic is to administer a dose of thrombolytic agent that only partially dissolves the thrombus. Following this, palliative therapy is

administered while the cat's inherent fibrinolytic system breaks down the remaining thrombus more slowly. This has been achieved clinically with a loading dose of 90,000IU of streptokinase followed by 34,000IU/hour for three hours. Although efficacy was difficult to judge, some cases appeared to benefit from this approach (Kittleson 1998).

**ii. Recombinant tissue type Plasminogen Activator (tPA)**

Tissue type plasminogen activator has greater specificity than urokinase or streptokinase as it converts only fibrin-bound plasminogen to plasmin, initiating local fibrinolysis with limited systemic proteolysis. Like plasminogen, tPA has a high affinity for fibrin within thrombi so both tPA and plasminogen bind fibrin in close proximity to each other, potentiating the tPA catalysed conversion of plasminogen to plasmin at the site of the thrombus. Due to its higher specificity there is less chance of haemorrhagic complications compared with streptokinase (Pion & Kittleson 1989, Behrend *et al* 1996, Rush *et al* 1998) but streptokinase and tPA have equal potential for causing reperfusion syndrome (Killingsworth *et al* 1986, Pion & Kittleson 1989, Rush *et al* 1998, Fox 1999, Rodriguez & Harpster 2002).

Administration of tPA at a dose of 0.25 to 1.0mg/kg/hour for a total intravenous dose of 1 to 10mg/kg has been described (Pion 1988, Pion & Kittleson 1989, Rush *et al* 1998, Fox 1999; 2000, Thompson *et al* 2001, Rodriguez & Harpster 2002). In one study successful thrombolysis was defined as reperfusion within 36 hours of tPA administration and was reported in 50% of cats with TE; 43% of treated cats survived the therapy and ambulated within 48 hours of presentation (Pion 1988, Pion & Kittleson 1989). While tPA effectively reduced the time to reperfusion and return to function, 50% of cats died during therapy raising concerns regarding rapid thrombolysis and the safe and effective doses of tPA. The reported complications during therapy arose from reperfusion syndrome (70%), CHF (15%) and sudden death (15%) (Pion & Kittleson 1989). No placebo treated cats were included in this study so no definitive conclusions of risks versus benefits can be made. Fifty percent of cats treated with cage rest and aspirin, at a dose of 25mg/kg every third day, regained function within six weeks further raising concerns regarding the proposed benefits of early reperfusion and the possible increase in mortality associated with tPA administration (Pion 1988, Pion & Kittleson 1989).

Unlike streptokinase, tPA has a short half life and must be administered in conjunction with heparin to prevent acute re-thrombosis (Kittleson 1998). It has been reported that 90% of cats successfully treated with tPA re-thrombose within one to three months (Kittleson 1998) despite aspirin, heparin and warfarin administration. Further widespread, controlled clinical trials in cats with aortic TE are necessary to assess the efficacy and risks associated with thrombolytic therapy versus other standard therapies.

**(7) Anti-coagulant Therapy**

Anti-coagulants used in the treatment of aortic TE (heparin and warfarin) have no effect on established thrombi. Their use is based on the premise that by retarding synthesis of coagulation factors or accelerating inactivation of clotting factors, thrombosis from activated clotting pathways can be prevented by altering the thrombotic balance. In cats that have suffered a previous TE or in those considered at high risk of thrombosis, oral anticoagulants may offer a reduced risk of thrombosis. However, they also increase the risk of haemorrhage so it should not be attempted without appropriate monitoring of coagulation parameters and careful patient selection.

**i. Heparin**

Initial anti-coagulant therapy involves the use of the co-factor heparin which acts by complexing with antithrombin III (AT III), enhancing its ability to neutralise activated clotting factors (IX, XI, X and XII) and thrombin (II) and so preventing further activation of the coagulation process. It prevents further formation and expansion of thrombi and so allows thrombolytic processes to dissolve the existing thrombus. The efficacy of heparin in treating cats with spontaneous TE has not been established and reported dosages vary widely. One reported dosage regime for heparin sodium is 50IU/kg iv which is repeated every six to eight hours (Laste & Harpster 1995, Sisson & Thomas 1995, Fox 2000). An alternative dosage regime is 100 to 200IU/kg iv followed by 50 to 100IU/kg sc every six to eight hours (Fox 1999, Rodriguez & Harpster 2002). In both cases the dose is then adjusted to prolong the activated partial thromboplastin time (APTT) to 1.5 to 2.0 times the baseline pretreatment value (Pion & Kittleson 1989, Fox 1999; 2000, Rodriguez & Harpster 2002) or the partial thromboplastin time (PTT) to 2.0 to 2.5 times the baseline value (Fox 2000). Clotting profiles must be carefully monitored as haemorrhage is a major complication.

Heparin may be administered by the subcutaneous or intravenous routes but repeat intramuscular injections are best avoided as local haemorrhage may result. Long term subcutaneous use of heparin for prevention of FATE has been described but data are not available to evaluate its effectiveness (Harpster 1986, Pion & Kittleson 1989). Heparin is destroyed in the gastrointestinal tract therefore it is not effective for longterm oral administration.

The most prevalent complication with heparin use is haemorrhage. If it occurs protamine sulfate can be administered as an effective antidote (Pion & Kittleson 1989). The reaction to protamine sulfate is almost instantaneous and lasts for approximately two hours. Dosages of protamine sulfate must be carefully selected as overdosage causes irreversible haemorrhage for which there is no known therapy. Protamine sulfate should be administered by slow intravenous injection with the dose rate dependant upon the time since the last heparin administration and the heparin dose. If given less than one hour after administration of heparin, the dosage of protamine sulfate is 1mg per 100IU of heparin. If one hour has elapsed since the last heparin dose, the protamine sulfate dose is halved. If two hours has elapsed, 0.25mg of protamine sulfate per 100IU of heparin should be administered (Pion & Kittleson, 1989).

**ii. Low Molecular Weight Heparin (LMWH)**

In recent years there has been some interest in the use of fractionated heparins called LMWHs for the treatment and/or prevention of FATE (Baty 2001, Rodriguez & Harpster 2002). As a consequence of the smaller molecular size and structure of these compounds, they have less specificity for inhibiting thrombin (Weitz 1997, Baty 2001, Rodriguez & Harpster 2002) but retain their specificity for coagulation factor X (Weitz 1997, Rodriguez & Harpster 2002). In addition, LMWHs have lower binding capacity for proteins, endothelial cells and macrophages, i.e. they have higher bioavailability than unfractionated heparin (Weitz 1997, Baty 2001, Rodriguez & Harpster 2002). These properties would be expected to provide a lower potential for haemorrhage and allow for once daily or twice daily subcutaneous administration which can be done at home (Weitz 1997, Baty 2001, Rodriguez & Harpster 2002). The use of LMWHs in humans is well established for antithrombotic therapy (Weitz 1997, Thompson *et al* 2001, Baty 2001, Rodriguez & Harpster 2002) and they have less inhibitory effect on collagen-induced platelet activity compared with unfractionated heparins (Goodman *et al* 1999, Baty 2001). Laboratory monitoring is less critical with LMWHs as their antithrombotic effects and pharmacokinetics are more predictable than unfractionated heparin (Weitz 1997, Baty 2001, Rodriguez & Harpster 2002). Recent data have, however, suggested that they may be less efficacious in the treatment or prevention of arterial compared with venous TE in people (Baty 2001).

In a preliminary study, examining the effects of LMWHs on antifactor Xa activity and APTT in normal cats, it was suggested that dalteprim sodium can be effectively given at a dose of 100IU/kg sc once daily (Goodman *et al* 1999, Baty 2001, Rodriguez & Harpster 2002). LMWHs are mainly excreted through the kidneys hence patients with renal insufficiency should be monitored for unwanted prolongation of coagulation parameters. As with most FATE therapies controlled data are now required to make objective recommendations on the clinical use of LMWHs in cats with TE or as prophylaxis.

**iii. Warfarin**

Warfarin is used as long term maintenance anticoagulant therapy to prevent TE episodes (Pion & Kittleson 1989, Harpster & Baty 1995, Rush *et al* 1998, Fox 1999; 2000, Baty 2001, Rodriguez & Harpster 2002). It acts by impairing hepatic vitamin K which is essential for the synthesis of coagulation factors II, VII, IX and X and anticoagulant proteins C and S. There is some discrepancy in the literature as to which cats should be treated with warfarin. Some propose it for chronic oral maintenance in cases of advanced myocardial disease, with or without a prior TE event, while others advise more caution or restrict its use to cases with aortic TE. Others recommend warfarin prophylaxis for all cats with M mode-derived LA:Ao ratios of greater than or equal to 2.0, even in the absence of a prior TE event (Harpster & Baty 1995) or, with the presence of swirling, highly echogenicic spontaneous contrast in the LA (Harpster & Baty 1995, Laste & Harpster 1995). All agree that warfarin therapy should not be attempted in the absence of frequent monitoring of coagulation parameters and should only be considered for indoor cats due to the higher risk of haemorrhage.

The clinical effectiveness of warfarin in cats is not known and there is currently inadequate controlled data to determine whether there is an acceptable risk to benefit ratio (Harpster 1986, Pion & Kittleson 1989, Sisson & Thomas 1995). There is also variation in the recommended starting dose of warfarin: 0.2-0.5mg/cat/day (Sisson & Thomas 1995), 0.25-0.5mg/cat/day (Rush *et al* 1998, Fox 1999; 2000, Rodriguez & Harpster 2002), 0.06-0.1mg/cat/day (Pion & Kittleson 1989), 0.5mg/cat/day (Harpster & Baty 1995). The initial dose of warfarin is then adjusted to maintain coagulation system parameters within certain parameters. As much as 20-fold variability in dose response has been reported in humans and significant variability has been observed with warfarin therapy in cats (Harpster & Baty 1995).

Historically oral anticoagulant therapy has been monitored by the prothrombin time (PT) which measures the activity of coagulation factors II, VII and X. The proteins induced by vitamin K antagonists (PIVKA) test, which detects the presence of inactive precursors of clotting factors II, VII, IX and X, is now considered to be the assay of choice if available (Pion & Kittleson 1989). The initial dose of warfarin is adjusted to maintain the clotting time at twice the baseline value at 8 to 10 hours post dosing. Alternatively, the warfarin dose can be adjusted using the International Normalisation Ratio (INR) to maintain a value of 2.0 to 3.0 (Harpster & Baty 1995, Fox 2000).

$$INR = [\text{ Cat PT} - \text{Control PT }]^{ISI}$$

Where, ISI is the international sensitivity index which should be provided by the chosen laboratory. This calculation allows the PT to be adjusted for variations in the thromboplastin reagent and laboratory technique (Fox 1999, Baty 2001). The maintenance dose of warfarin should be monitored daily for the first three days during initial titration, then every other day (twice) and then weekly until a safe and stable dosage regime is determined (Pion 1988, Pion & Kittleson 1989). It can take up to a week for new steady state conditions to be achieved. The therapeutic effect should then be re-evaluated at least once per month (Pion 1988, Pion & Kittleson 1989). However, in humans it has been reported that there is a lack of correlation between clotting times and the incidence of re-thrombosis or bleeding on warfarin therapy (Pion & Kittleson 1989). Warfarin therapy should ideally be overlapped with heparin therapy for three to four days as approximately 72 hours is required to reduce the concentration of existing clotting factors. No clinical studies have been conducted to evaluate the optimal time for this overlap (Harpster & Baty 1995, Fox 2000). In addition to its effect on clotting factors, warfarin also reduces levels of protein C, a naturally occurring anti-coagulant with anti-inflammatory properties (Fox 1999; 2000). Protein C has a short plasma half life and therefore, in the early stages of warfarin therapy, there is the potential for the development of a hypercoaguable state before other vitamin K dependant factors are affected necessitating

the overlap with heparin therapy (Harpster & Baty 1995, Fox 1999; 2000).

A trial was conducted on warfarin therapy in a group of 25 cats considered to be at risk of developing TE (Harpster & Baty 1995); 23 of these had suffered a prior TE event and the remaining had a LA:Ao ratio greater than 2.0. Warfarin was initiated at 0.5mg/cat/day and overlapped with 100IU/kg of heparin three times daily for three to four days. Warfarin doses were then adjusted according to coagulation parameters. The most common complication encountered was recurrent TE in 43.5% of cases. Other complications included bleeding episodes (20%), symptomatic CHF (12%) and sudden death of undetermined cause (12%). Overdosage with warfarin can have disastrous results hence it must be used cautiously and only in patients that can be monitored

**TREATMENT AND PREVENTION OF FELINE AORTIC THROMBOEMBOLISM**

| Drug | Indications | Dosage | Side effects, comments |
|---|---|---|---|
| Aspirin | Long term therapy to prevent thrombus formation | 25mg/kg po q48-72 hours | May cause gastrointestinal upset. |
| Warfarin | Long term therapy to prevent thrombus formation | 0.2-0.5mg po q24 hours (Sisson & Thomas 1995)<br>0.25-0.5mg po q24 hours (Rush *et al* 1998, Fox 1999, Fox 2000; Rodriguez & Harpster 2002)<br>0.06-0.1mg po q24 hours (Pion & Kittleson 1989)<br>0.5mg po q24 hours (Harpster & Baty 1995) | Variation in initial dose, monitor coagulation parameters to achieve optimum dosage.<br>May cause haemorrhage.<br>Numerous drug interactions. |
| Heparin | To prevent thrombus formation | 50IU/kg sc q6-8 hours (Laste & Harpster 1995; Sisson & Thomas 1995; Fox 2000)<br>100-200IU/kg iv followed by 50-100IU/kg sc q6-8 hours (Fox 1999; Rodriguez & Harpster 2002) | May cause haemorrhage, monitor coagulation parameters. |
| Streptokinase | Dissolve existing thrombus | Loading dose of 90,000IU iv over 20-30 minutes followed by 45,000IU constant rate infusion over 3 hours (Killingsworth *et al* 1986) | Non specific plasminogen activator, potential to cause systemic fibrinolysis/ haemorrhage.<br>Monitor for reperfusion injury (hyperkalemia and acidosis). |
| Tissue-plasminogen activator | Dissolve existing thrombus | 0.25-0.1mg/kg/hour iv constant rate infusion for a total dose of 1-10mg/kg (Pion 1988, Pion & Kittleson 1989, Rush *et al* 1998, Fox 1999, Fox 2000, Thompson *et al* 2001, Rodriguez & Harpster 2002) | Specific activator of fibrin-bound plasminogen thus less potential for haemorrhage.<br>Monitor for reperfusion injury (hyperkalemia and acidosis). |
| Hydralazine | Vasodilator | 0.5-0.8 mg/kg po q12 hours | Potential to exacerbate hypotension and hypothermia. |
| Acepromazine maleate | Vasodilator, sedative | 0.2-0.4mg/kg po, sc, im or iv q12 hours | Potential to exacerbate hypotension and hypothermia. |
| Butorphanol | Analgesic | 0.2-0.4mg/kg sc, im or iv q4 hours as required (Killingsworth *et al* 1986, Rodriguez & Harpster 2002) | Causes sedation. |
| Oxymorphone | Analgesic | 0.05-0.15mg/kg sc, im or iv q4 hours as required (Killingsworth *et al* 1986, Kittleson 1998, Rodriguez & Harpster 2002) | Can cause respiratory depression and bradycardia.<br>In cats may cause ataxia, hyperaesthesia and behavioural changes (without concomitant tranquillisation). |

*TABLE: Drugs commonly used in the treatment and prevention of feline aortic thromboembolism.*

closely and kept indoors to minimise the risk of haemorrhage.

**(8) Antiplatelet Therapy**

Exposure of blood to subendothelial connective tissue and damage to platelet membranes leads to rapid platelet activation, aggregation and subsequent thrombosis. Pharmacological measures are directed towards modifying platelet aggregation. Aspirin (acetyl salicylic acid) has theoretical benefits during and after a TE event to prevent further embolic events. It induces a functional defect in platelets through irreversible acetylation of cyclic oxygenase. This is an enzyme critical in converting arachadonic acid to thromboxane A2 (TXA2), a potent prostaglandin-like platelet aggregating substance which induces platelet activation through release of ADP and associated vasoconstriction (Pion & Kittleson 1989, Rush *et al* 1998, Fox 1999; 2000, Rodriguez & Harpster 2002).

Aspirin also inhibits cyclooxygenase in vascular endothelium and prevents the formation of prostacyclin, which inhibits platelet aggregation and induces vasodilation (Schaub *et al* 1977, Pion & Kittleson 1989, Fox 1999; 2000). The optimal dose of aspirin that will inhibit TXA2 production but spare vascular endothelial prostacyclin synthesis has not been established for cats (Fox 1999; 2000). However in low doses aspirin should not significantly effect synthesis of prostacyclin (Slappendel 1988). Aspirin is utilised therapeutically because of its different kinetics in the two systems. Inhibition of endothelial cyclooxygenase is reversible and the common practice of administering aspirin every third day may allow maximal platelet inactivation, while minimising endothelial cyclooxygenase inhibition and thrombotic tendencies.

In a review of current literature it is widely accepted that aspirin administered to cats at a dose of 25mg/kg every 48 to 72 hours inhibits platelet function for three to five days. There are however no clinical trials that evaluate the efficacy of aspirin in reducing the occurrence or recurrence of TE but there are short term experimental studies supportive of some beneficial effects. Greene (1985) demonstrated that 25mg/kg of aspirin effectively inhibits platelet aggregation and function for three to five days. Its use has also been demonstrated to improve collateral circulation in experimentally induced FATE (Schaub *et al* 1982, Greene 1985, Fox 1999) and, furthermore, pre-existing aspirin therapy has been shown to improve collateral blood flow developing around the occlusion (Schaub *et al* 1982).

Unfortunately in a clinical setting cats receiving aspirin therapy will often re-embolise (Pion 1988, Pion & Kittleson 1989, Sisson & Thomas 1995, Laste & Harpster 1995, Fox 2000, Baty 2001). This observation is consistent with the variable efficacy of aspirin prophylaxis in various forms of arterial thromboembolic disease in humans (Baty 2001). In one retrospective study most cats treated with aspirin re-embolised within six months (Laste & Harpster 1995) while in another only 17% suffered a recurrent episode (Schoeman 1999). The cats that did re-embolise supported the findings of Schaub *et al* (1982) who suggested that cats, suffering a TE event whilst on aspirin therapy high enough to inhibit platelet function, recover more quickly due to efficient collateral circulation (Schoeman 1999). Pion & Kittleson (1989) reported that 75% of cats treated with tPA re-embolised despite aspirin at 25mg/kg every third day. As the value of aspirin in preventing a first occurrence of cardiogenic emboli is unknown, and its value in preventing thrombus recurrence is doubtful, there is need for controlled, epidemiologically-based clinical trials to assess this therapy.

Propanolol has been suggested for the treatment of cats with an underlying cardiac condition predisposing to FATE. *In vitro* studies have shown that propanolol at a dose of 2.0 to 5.0mg had no effect on platelet aggregation in any cat to which it was administered 12 hours after administration (Greene 1985). It is possible that propanolol has properties which may not have a permanent inhibitory effect on platelet aggregation and/or its effect was cleared from the blood in less than 12 hours.

## SUMMARY

Feline patients with cardiac disease or prior TE event(s) should be considered at risk of developing intra-cardiac thrombi and signs of distal arterial thrombosis. Prevention of peripheral thrombosis is one of the most important and complex therapeutic objectives in managing cats with cardiac disease. The ideal means of minimising/preventing thrombosis is the resolution of underlying cardiac disease where possible or correction of the pathophysiologic alterations caused by or coincident with cardiac disease which place such cats at risk. Prevention of FATE also becomes more complex when it is considered that not all cases are associated with cardiac disease. Several cats treated for well documented FATE had no auscultatory, radiographic or echocardiographic cardiac abnormalities. In these cases the risk of FATE is impossible to predict and prevent with our current state of knowledge.

Well substantiated and effective therapeutic recommendations for the prevention of FATE have not been identified. Currently it would appear that the most feasible option for prophylaxis is to attempt to manipulate the patient's coagulation system in an effort to alter the balance between prothrombotic pathways and those which inhibit thrombus formation, to reduce the thrombogenic potential. Large scale studies are required to evaluate epidemiology, risk factors and the aetiopathogenesis of FATE. Multi-centre, clinical trials have not yet been performed to evaluate the optimal therapeutic strategy (Fox 2000) and are necessary before further conclusions can be made about therapy for prevention, for FATE or for prophylaxis against further TE events.

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