

Scientific Electronic Archives

Issue ID: Sci. Elec. Arch. Vol. 11 (6)

December 2018

Article link

<http://www.seasinop.com.br/revista/index.php?journal=SEA&page=article&op=view&path%5B%5D=714&path%5B%5D=pdf>

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**Thromboembolism arterial feline – literature review**

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Abstract. Thromboembolism is characterized by the obstruction of a vessel caused by a blood clot formed elsewhere and transported with the bloodstream. This syndrome occurs in felines and is usually associated with hypertrophic cardiomyopathy, facilitating the formation of thrombi in the interior of the atrium or left ventricle. It occurs more frequently in middle aged male cats with no defined breed, probably because they are most affected by cardiomyopathy. Clinical signs are usually acute, secondary to tissue ischemia, and are related to the site of obstruction. The diagnosis is based on the characteristics found in the physical examination and anamnesis, with frequent paralysis of acute pelvic limbs, cold limbs and cyanotic cushions. Treatment consists of preventing the formation of new thrombi, improving pain, controlling hypertrophic cardiomyopathy or severe arrhythmias and supportive treatment.

Keywords: thrombus, vascular, coagulation

Contextualization and analysis

A thrombus is a blood clot formed when there is a vascular injury, circulatory stasis presence of and / or alterations in blood coagulation (Fox et al., 1999; Couto, 2010).

To cause the formation of thrombus, endothelial damage is required to release serotonin and thromboxane. Several factors can cause endothelial injury, including, sepsis, systemic inflammatory disease, cancer, trauma, cardiomyopathies and reperfusion injury. The thromboxanes, thromboxane A² specifically, are released by stimulation of adenosine diphosphate which are present on the platelet membrane, this substance causes vasoconstriction and stimulates the further process of platelet aggregation (Ettinger & Feldman, 2005).

The cats, compared with other species appear to blood hypercoagulability a status, leading to increased platelet reactivity because its platelets have higher concentrations of serotonin, in which factor induces platelet aggregation. They also have high concentrations of fibrinogen and factor VIII and / or deficiency of factors of thrombus inhibitors such as antithrombin III (Ettinger & Feldman, 2005).

The main elements for the thrombus formation are the platelets, forming the "white thrombus" with decreased blood flow erythrocytes are added to the thrombus, forming the "red thrombus". With the increased cardiac chamber is decreased blood flow, tending circulatory stasis and

promoting the aggregation erythrocytes and coagulation factors (Ettinger & Feldman, 2005).

Thromboembolism (TE) tends to occur when alter the normal hemostatic processes, creating conditions for formation of a clot or preventing thrombolysis (Ware, 2010). The development of arterial thromboembolism occurs when a piston comes off of a present thrombus normally, in the left atrium and left ventricle, get in into the peripheral circulation, and be accommodated in a vessel that has a smaller diameter than the plunger light. Then the forcer blocks the artery vasoconstriction and promotes side vasoconstriction (Shoeman, 1999; Smith & Tobias, 2004).

Besides the addition to the endothelial injury, circulatory stasis or some coagulation disorders may also promote thrombus formation. These pro-thrombotic factors are called Virchow's triad, present in cardiomyopathy how so predisposing the formation of thrombs in cardiac cats (Smith & Tobias, 2004; Ettinger & Feldman, 2005). Any of these conditions or the junction of them predispose the feline to the thromboembolism, in addition, the collateral circulation is modulated by vasoactive substances secreted by endothelial clot and the substrate, reducing the movement exacerbates ischemia (Fox, 2007).

To occur thromboembolism it is required to occur side vasoconstriction induced by the release of vasoactive substances such as serotonin and thromboxane promoted the thrombus, jeopardizing

the proper limb perfusion. Studies indicate that only ligation of the distal aorta does not reproduce the episode of arterial thromboembolism, proving that collateral circulation has fundamental effect on the manifestation of thromboembolism (Ware, 2010). Imhoff (1961) demonstrated in study, that the experimental induction of serotonin in aortic blindly bag surgically created, leads to vasoconstriction and ischemic side neuromyopathy.

In cases of thromboembolism, ischemic neuromyopathy can be found with obstructed blood flow and vasoconstriction of the collateral circulation occurs in the degeneration of myelin sheaths and consequent impairment of nerve conduction, leading to dysfunction in peripheral nerves. If the circulation is not restored within five to six hours, the damages can be irreversible (Fox et al., 1999; Ettinger & Feldman, 2005; Couto et al., 2010).

Clinical signs depend on five factors: the location of the forcer, the severity and duration of the occlusion degree of functional collateral circulation, the state of the myocardial function and the development of complications (Fox, 2007).

Generally clinical symptoms are acute in the beginning, secondary to tissue ischemia. The symptoms are related to the infarcted local: renal ischemia (azotemia), cerebral ischemia (brain lesion), paralysis / paresis (ischemia in the regions supplying the fore and hindlimbs) (Couto et al., 2010).

Over 90% of cases the hind limbs are most commonly affected (Figure 1) (Fox, 2007), may be monolateral when the piston blocks vessels of only one member, or bilateral when there is a piston mainly in the trifurcation of distal aorta (Piston saddle) (Ettinger & Feldman, 2005; Couto, et al., 2010).

The most common complaints are acute pain, cold extremities affected and pale to cyanotic, paresthesia, paralysis and absence of femoral arterial pulse (Fox, 1992).

In the first 10 to 12 hours ischemia causes swelling and myalgia in the gastrocnemius and tibial muscles. 24 to 72 hours of acute crisis, muscle stiffness ceases. With the involvement of sensory nerves and loss of its function, and the pain tends to decrease. The nail beds tend to not bleed when cuted. There may be no deep pain in the hind limbs and tail, depending on the severity of the condition (Smith & Tobias, 2004; Fox, 2004; Ettinger & Feldman, 2005; Tobias & Fine, 2009; Tilley, 2011). Most cats are clinically dehydrated and hypothermic (Fox, 2007). Not seen any manifestation of cardiomyopathy so far before the thromboembolic event during hospitalization that animals begin to show symptoms of heart failure (Smith & Tobias, 2004; Ettinger & Feldman, 2005).

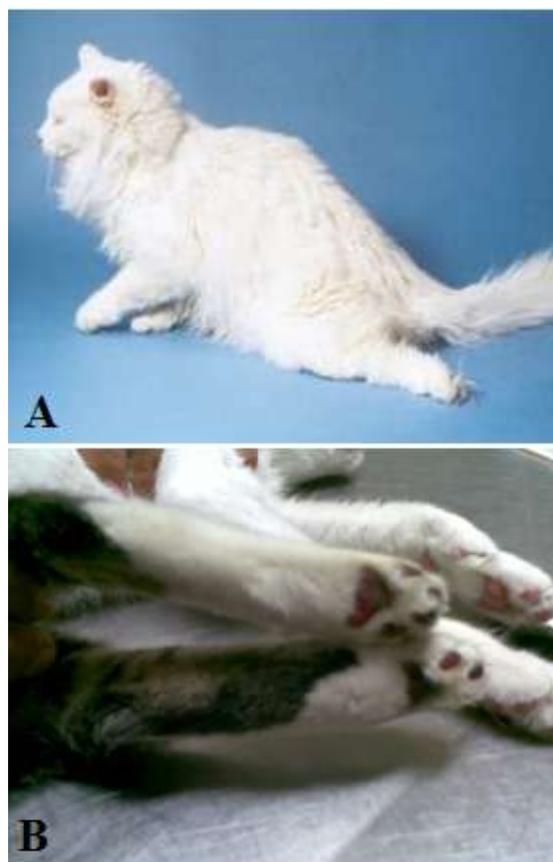


Figure 1: A. Feline with thromboembolism in the aorta distal, with paresis of the hind limbs. (Source: Couto et al., 2010). B. cushions plantar cyanotic compared with cushions palm. (Source: Addeo, 2011).

Cats with heart disease have signs such as arrhythmias, systolic murmurs, gallop and cardiomegaly. Dyspnea, tachypnea, open mouth breathing, can be symptoms of pain or heart failure (Laste & Harpster, 1995; Fox et al., 1999; Smith & Tobias, 2004; Ettinger & Feldman, 2005). Ware (2010) refers to other clinical findings that might be evident in cats with thromboembolism:

- scroll Movement;
- Vocalization by discomfort / pain;
- Anorexia;
- Lethargy / weakness;
- Hematological and Biochemical changes;

Together electrolyte changes may occur, however, not being also consistent with thromboembolism. May find hypercalcemia resulting from reperfusion injury of skeletal muscles after thromboembolic event, hypokalemia may be present for administration of diuretics in some cases of heart disease or the presence of anorexia (Fox, 2004; Smith & Tobias, 2004).

In more severe cases, there may be cardiogenic shock, when present some heart disease that may have originated the thrombus, or distributive shock due to the fall of vasomotor tone, occlusion of the vascular bed and release of vasoactive substances (Smith & Tobias, 2004; Ware, 2010).

According to Ware (2010), metabolic acidosis, electrolyte abnormalities, disseminated

intravascular coagulation (DIC) and hyperglycemia are common in cases of thromboembolism.

Early diagnosis begins with the physical examination and anamnesis, they are often reported acute paralysis of hind limbs, cold limbs and cyanotic or pale cushions. Vocalization, pain and anorexia are also found (Tilley, 2011).

When cutting unguis layer, does not occur bleeding or blood can come out with dark color, confirming the poor perfusion (Ettinger & Feldman, 2005).

The diagnosis is based on the found characteristic on physical examination. The femoral pulse is often reduced or absent, moreover, the measurement of the temperature is essential for the diagnosis and prognosis of the patient (Smith & Tobias, 2004).

In a retrospective study by Smith et al. (2003), where 127 cases of thromboembolism were analyzed, it was observed that the rectal temperature influence on the survival of approximately 75% of patients, hypothermia increased mortality rates. The same study demonstrated that the survival rate of infected felines by arterial thromboembolism was 37%, and animals that survived the first episode had recurrence rate of 25 to 45%.

Ultrasonography with color Doppler can show the exact location of the piston and sizing. The venous or arterial angiography is most recommended for location of thrombi, but requires general anesthesia, complicating its use. The measurement of blood pressure of the affected limb can assist the diagnosis, since in case of thromboembolism pressure will be low if the thrombus partially obstruct the vessel, or even no pressure if there is complete obstruction (Fox et al., 1999; Ettinger & Feldman, 2005).

Echocardiography it's a viable and non-invasive option for cardiac evaluation of patients with thromboembolism, since the vast majority of cases occur by cardiac abnormalities. The detection of intracardiac thrombi also adds in the diagnosis (Figure II). They can also be observed hypertrophic cardiomyopathy with left ventricular hypertrophy, large left atrium and hypercontractility (Fox et al., 1999; De Francesco, 2003; Ettinger & Feldman, 2005). Still can be observed restrictive and dilated cardiomyopathy. Regardless of the type of cardiomyopathy, more than 50% of patients have increased left atrium (De Francesco, 2003).

Chest x-rays can be used to detect cardiopulmonary abnormalities, commonly show signs of congestive heart failure and pulmonary edema, pleural effusion and cardiomegaly. Also can be related diseases such as, heartworm disease or cancer can still be observed. However, some cats may not show any radiographic changes that evidences a cardiomyopathy (Ware, 2010).

The electrocardiographic examination can be used to detect arrhythmias, conduction disturbances, ventricular tachycardia, supraventricular tachycardia, sinus tachycardia, extrasystoles, among others.

These disorders may be caused by electrolyte imbalance, principally of hypercalcemia resulting from reperfusion syndrome (Ettinger & Feldman, 2005).



Figure II: echocardiographic image, showing thrombus (arrow) in the left atrium. Source: Tilley et al, 2011.

The laboratory tests are useful to assist in diagnosis. Usually cats with thromboembolism show changes ALT, AST, CK and LDH, for liver and skeletal muscle damage. Besides azotemia by renal ischemia. With respect to the coagulation profile, the extension fibrolytic activity markers as D dimer and fibrinogen degradation product (PDF) can be changed, with the result that positive D-dimer results in ischemic activity parenchymatous organs (Harpster & Laste 1995; Ettinger & Feldman, 2005). Relative the biochemical changes can occur azotemia by renal ischemia, increased activity of the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), the changes of these enzymes occur by inflammation and hepatic necrosis and skeletal muscle, starting in 12 hours thromboembolism after reaching peak levels at 36 hours. The same way, there is change in creatine kinase (CK) and lactate dehydrogenase (LDH) by widespread damage to skeletal muscles (Smith & Tobias, 2004; Fox, 2004; Tobias and Fine, 2009; Ware, 2010). However, some cats may show no radiographic change that evidences a cardiomyopathy (Ware, 2010).

Treatment consists in controlling hypertrophic cardiomyopathy or severe arrhythmias, nutritional support treatment of hypothermia correction and prevent self-mutilation, measures to limit the growth and thrombus formation, improvement of acute pain, prevention of repeated events and critical control (Fox, 2007).

The prevention of thrombogenesis is made by the administration of antithrombotic and anticoagulant agents. These agents do not have the established thrombus destruction of function, but to prevent and avoid the formation of new thrombi while the thrombolytic system acts to destruction of

obstructive piston (Laste & Harpster, 1995; Smith & Tobias, 2004; Ettinger & Feldman, 2005).

The medications, are Often used to Prevent acetylsalicylic acid (ASA), which acts in the inhibition of platelet aggregation. This drug inhibits cyclooxygenase, by reducing the synthesis of prostaglandins and thromboxane A², reducing platelet aggregation, vasoconstriction and the release of serotonin. The ASA is indicated for cases in which the patient is able to tolerate oral administration of drugs (Ware, 2010). The recommended doses isn't completely established, but De Francesco (2003) proposes to administer a tablet of 81 milligrams (mg) per animal, orally, every two or three days. Studies have shown the same effect using lower doses of 5 mg / animal every 72 hours being preferred for reducing the risk of side effects (Smith & Tobias, 2004). However, Moraillon (2013) recommends a dose of 1 mg / kg every two days in cats affected by cardiomyopathies.

According to Fox (2007), clopidogrel it is under evaluation for prevention and treatment of arterial thromboembolism, being a potent antiplatelet. It is an irreversible antagonist of the receptor platelet adenosine diphosphate, being a primary and secondary inhibitor of platelet aggregation. The antiplatelet effects occur in three days after administration. The recommended dose for every 24 hours is 18.75 mg per animal. They may experience side effects such as nausea, vomiting and diarrhea. In relation to the anticoagulant therapy the indicated drug is heparin sodium to reduce thrombotic formation preventing further activation of the coagulation cascade. Warfarin can be used, but its use is controversial due to the high hemorrhagic and teratogenic potential (Smith & Tobias, 2004; Ware, 2010).

Heparin has an anticoagulant action primarily by binding at the site of lysine on antithrombin III. It also stimulates the release of tissue factors in vascular sites, reducing the activation of the extrinsic coagulation cascade. It's not recommended administration because the risk of bleeding at the injection site is recommended (Fox, 2004; Ware, 2010; Tilley, 2011). It can be used the initial protocol usually 250 to 375 IU / kg, IV, followed 150-250 IU/kg/SC every 6 to 8 hours (Ettinger & Feldman, 2005). However Moraillon (2013), proposed in urgent cases a dose of 500 IU intravenously with renewal of subcutaneous dose after 3 to 8 hours. Couto (2010), describes the initial protocol with a dose of 150 to 200 IU/kg, subcutaneously administration every 6 to 8 hours by 2 to 4 days.

Thrombolytic therapy may be administered to try to dissolve the thrombus, for helping to facilitate fibrinolysis, plasminogen conversion into plasmin, if started within 4 hours of thrombus formation your chances of success are maximized. This can be done by systemic infusion or local directly on the thrombus (Santos, 2008; Dunn, 2011). The streptokinase, urokinase and the enabler

of human recombinant tissue plasminogen activator (rt-PA) has been administered in cats with arterial thromboembolism with 35-42% survival rates. The protocol used for administration of streptokinase is 90.000UI for 20 to 30 minutes, followed by continuous infusion of intravenous 45.000UI / h for three hours (Fox, 2007; Santos, 2008). Moraillon (2013), recommends intravenous infusion of 20,000 units / kg in 50 mL of isotonic saline.

For tissue plasminogen activator dose for intravenous administration is from 0.25 to 1mg/kg /hour (Fox, 2007; Santos, 2008). However, although these to fragment drugs effectively, clots, complications related to hemorrhage, reperfusion injuries (which may cause hypercalcemia and metabolic acidosis), cost of care, intensive care needs and high mortality prevent its widespread use (Ware, 2010). Surgical removal of clots, isn't recommended, especially at high surgical risk and when performed surgery is likely to have already been significant neuromuscular ischemic injury. The removal of the clot using embolectomy catheter, wasn't very effective in cats (Ware, 2010).

However, Dunn (2011) believes that the multimodal approach, using antithrombotic, anticoagulant and thrombolytic therapy, reconciled with the local intervention with the use of "stent" may be the best endovascular management for cases of thromboembolism.

Fox (2007) refers the treatment of pain, especially within 24 hours of thrombus formation, because after this period of pain seems to significantly decline, caused by nerve injury. Should be avoided drugs that reduce mental, physical and appetite. Butorphanol can be used for the treatment of pain in a dose of 0.2 at 0.4 mg / kg / SC every 6 to 8 hours. Although, Tobias & Fine (2009), reported that the effect of butorphanol has a low and short duration, suggesting the use of opioids.

Fentanyl patches in dosage of 25 æg / hr can relieve pain for up to three days, however, it is required 12 hours to get the expected analgesic effect (Fox, 2007). The supportive care must be provided in order to improve and maintain adequate levels in tissue perfusion and minimize the occurrence of new lesions and to improve the organ function (Ware, 2010). It must be restored the circulating oxygen levels in cases of breathing difficulties. Monitor the occurrence of electrolyte imbalances. Stimulating collateral circulation with massage muscles. To improve systemic perfusion. In cases of heart failure initiation of treatment (Fox, 2004; Tilley, 2011).

Not should be used the drugs:

- Propranolol, for not selective B-blocking effect may assist in peripheral vasoconstriction mediated by alpha receptors, thereby preventing collateral blood flow (WARE, 2010; Tilley, 2011).
- Acepromazine, should also not be used because it is only effective in blocking alpha-adrenergic receptor, promotes vasodilation and no improvement

collateral flow, and may cause hypotension (WARE, 2010; Tilley, 2011).

The prognosis it's often bad for most cases (DeFrancesco, 2003). The rapid identification and treatment of thromboembolism improve the prognosis, however, the recurrence of worsening TE (Ware, 2010; Dunn, 2011).

Keeping the collateral circulation is essential in clinical resolution of thromboembolism (Tilley, 2011).

Only a third of individuals survives the initial episode. The survival is better when there is involvement of only one member or preservation of motor function (Ware, 2010).

Other factors that influence prognosis, is the location of thrombus, basic condition, and the clinician's ability to discover the basis disease (Dunn, 2011).

According to Smith, et al. (2003), the most common cause of death or euthanasia was inadequate control of congestive heart failure. Most cats do not respond well to treatment or die from the underlying cardiomyopathy (Dunn, 2011).

Final considerations

It can be seen that the thromboembolism is an emergency in clinical small animal. The TE is often associated with cardiomyopathy in cats, especially in hypertrophic. The diagnosis is made primarily by clinical signs, which are classic.

The treatment, the faster start, the greater the chances of survival for the animal because it reduces the complications caused by ischemia caused by the lack of movement on site. Prophylactic treatment is recommended, especially in patients who have been diagnosed with some heart disease or geriatric patients, who often present even though asymptomatic heart disease. It can be used for this treatment, clopidogrel, aspirin, or warfarin.

However, more research is needed to establish the correct dose of medication, therapy and what is the most appropriate. Apparently, the multimodal therapy seems to be the best management for animals with thromboembolism.

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