Dirofilaria immitis and D. repens in dog and cat and human infections

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Heartworm (Dirofilaria immitis) disease in dogs

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Heartworm disease in dogs

Introduction

Despite the name “heartworm” suggests a primitive cardiac involvement, the main localization of the worms and the first damages are in pulmonary arteries and heartworm disease should be considered as a pulmonary disease that in the last stage only involves the right cardiac chambers.

Few days after heartworms reach caudal pulmonary arteries, endothelial cells become swollen with wide intercellular junctions and disoriented longitudinal axes, as response to the trauma. Activates neutrophiles adhere to the endothelium surface and enter the space between endothelial cells. Furthermore, as linear areas of sub endothelium are exposed, platelet adhesion and activation is greatly stimulated. Damaged arterial surface allows albumin, plasma fluid and blood cells to reach the perivascular space.

After the endothelial changes, the intima thickens with fluid, leukocytes invade the wall and smooth muscles cells multiply within tunica media and migrate toward the endovascular surface as response to growth factor released by platelets. The multiplication and migration of smooth muscle cells cause the presence, on the internal arterial surface, of villi which are made by smooth muscle cells and collagen and covered by endothelial like-cells (Rawlings, 1986; Calvert and Rawlings, 1988). The gravity of villous proliferation is directly related to duration of infection and worm burden. The arterial surface of heavily infected dogs and cats appear rough and velvety, and both the lumen and the compliance of the pulmonary arteries are reduced.

Lung disease occurs secondary to vascular changes. Fluid and protein leaking through the vessel wall of affected arteries produce oedema in the parenchyma. Spontaneous death of some worms can produce thromboembolism and severe inflammatory reactions.

The reduction of compliance and gauge of pulmonary arteries, that can be also occluded by either thromboembolism or severe villous proliferation (Fig. 1), results in a hypertensive pulmonary state and, as a consequence, in an increased after load for the right ventricle which can induce “cor pulmonare” and right cardiac congestive heart failure. Protein and fluid leaking through the vessel wall of affected arteries produce further oedema and inflammation in the parenchyma (Dillon et al., 1995).

Based on the pathogenesis the clinical evolution of heartworm disease in dogs is usually chronic. Most infected dogs do not show any symptoms of the disease for a long time, months or years, depending on worm burden, individual reactivity and exercise, as arterial damages are more severe in dogs with

![Fig. 1. Right ventricle outflow tract and pulmonary artery of a dog with severe heartworm infections. Note the large worm burden and the villous proliferation of the pulmonary artery endothelium.](image)
intensive exercise than in dogs at rest (Dillon et al., 1995). Signs of the disease develop gradually and may begin with a chronic cough.

Coughing may be followed by dyspnoea, from moderate to severe, weakness, and sometimes lipohydramia after exercise or excitement. At this time abnormal pulmonary sounds (crackles) over the caudal lung lobes and second heart sound splitting can be often heard. Later, when right cardiac congestive failure is developing, swelling of the abdomen and sometimes legs from fluid accumulation, anorexia, weight loss, dehydration, is usually noted. At this stage, cardiac murmur over the right side of the thorax due to tricuspid valve insufficiency and abnormal cardiac rhythm due to atrial fibrillation are common findings. Sudden death rarely occurs and usually it happens following respiratory distress or cachexia.

In the chronic pathway of the disease sometimes acute symptomatology may occur. After severe spontaneous thromboembolism following the natural death of many heartworms, dogs may show acute life threatening dyspnoea and haemoptysis.

In small sized dogs is furthermore a common event the displacement of adult worms from pulmonary arteries to right cardiac chambers due to pulmonary hypertension and sudden fall in right cardiac output. In this case dogs affected shows the so called “caval syndrome”. Dyspnoea, tricuspid cardiac murmur and emoglobinuria (due to mechanical haemolysis in right cardiac chambers) are the most typical signs and fatal outcome is usual (Kitagawa et al., 1987; Atwel and Buoro, 1988; Venco, 1993).

### Diagnosis

Diagnosis of heartworm infection can be made in dogs by blood test detecting circulating microfilariae or adult antigens but further diagnostic procedures are usually required to determine the severity of disease and which is the best treatment (Knight, 1995).

#### Blood test for microfilariae

Blood sample is examined after concentration (Knott or Difill test) for the presence of microfilariae. If microfilariae are seen and identified as *D. immitis*, based on morphology that is considered a definitive proof of infection (specificity 100%). However up to 30% of dogs do not have circulating microfilariae even though they harbour adult worms, due to the presence of only worms of the same sex (quite unusual in dogs), immune reactivity of the host to microfilariae or administration of microfilaricidal drugs. The sensitivity of test for microfilariae is not therefore considered sufficient to rule out the infection in case of negative test.

#### Blood test for adult female antigens

Tests designed to detect heartworm adult antigens based on ELISA or colloidal gold staining techniques are considered highly specific as cross reactivity with other dogs parasites (i.e. *D. repens*, *Dipetalonema* sp.) does not occur.

These tests allow detection of adult heartworm antigens produced only by female worms and may provide information about worm burden (Knight, 1995; Venco et al., 2003). The sensitiv-
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The prevalence of heartworm disease is actually very high, but false negative results may occur in prepatent or very light infections or when only male worms are present (McCall, 1992).

Thoracic radiographs

Thoracic radiographs may show, in the advanced stage, enlargement of the pulmonary arteries, abnormal pulmonary patterns and in the worst cases right-sided cardiomegaly. If congestive right heart failure is present peritoneal and pleural effusion can be noted (Rawlings, 1986; Calvert and Rawlings, 1988). They are useful to assess the severity of the pulmonary lesions but not for evaluating worm burden (Venco et al., 2003). Since radiographic signs of advanced pulmonary vascular disease may persist long after an infection has run its course, some of the most severely diseased dogs may have disproportionately low worm burden (Fig. 2). On the contrary, some inactive dogs may have large worm burdens and be clinically asymptomatic with no or trivial radiographic lesions (Fig. 3).

Electrocardiography

As electrocardiogram displays the electrical activity of the heart, abnormalities, (electrical axis right deviation, atrial fibrillation) are usually found only in the last stage of the disease, when right cardiac chambers present severe damages.

Echocardiography

Echocardiography allows a direct visualization of cardiac chambers and connected vessels (Moise, 1988).

It also allows the visualization of parasites in right cardiac chambers, caudal vena cava, main pulmonary artery and proximal tract of both caudal pulmonary arteries (Fig. 4). The heartworms are visualized as double, linear parallel objects floating in the right cardiac chambers or into the lumen of vessels (Moise, 1988; Badertscher et al., 1988). It is performed mainly in cases where clinical and radiographic findings suggest severe disease. Cardiac ultrasound can increase the accuracy in staging the...
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disease and estimating the worm burden, both of which affect the treatment program and the prognosis.

Therapy

It has been said that the treatment of heartworm infection is difficult. There are several strategies that can be used including the option of not treating at all. The important concept to realize is that treating for heartworm infection is neither simple nor safe in itself.

Prior to therapy, the heartworm patient is assessed and rated for risk of developing post-adulticide thromboembolism.

Previously 4 classes were described in order to prevent the post-adulticide thromboembolism and give a correct prognosis (from class 1, low risk to class 4, very high risk) (Di Sacco and Vezzoni, 1992) but at present a more simple classification is usually preferred and the patient is included into one of two categories (low and high risk). Important factors include: how many worms are thought to be present based upon the ELISA tests performed and ultrasound examination (Venco et al., 2004), the size of the dog, the age of the dog (dogs ranging from 5 to 7 years are at high risk to harbour the largest worm burden; Venco et al., 2004), concurrent health factors, severity of the pulmonary disease, and the degree to which exercise can be restricted in the recovery period.

The categories into which patients are grouped are as follows:

**Low risk of thromboembolic complications** (low worm burden and no parenchymal and/or pulmonary vascular lesions)

Dogs included in this group must satisfy all this conditions:
- No symptoms
- Normal thoracic radiographs
- Low level of circulating antigens or a negative antigen test with circulating microfilariae
- No worms visualized by echocardiography
- No concurrent diseases
- Permission of exercise restriction

**High risk of thromboembolic complications**

In this group should be included all the dog that do not satisfy one or more of these conditions:
- Symptoms related to the disease (coughing, lipotimias, swelling of the abdomen)
- Abnormal thoracic radiographs
- High level of circulating antigens
- Worms visualized by echocardiography
- Concurrent diseases
- No permission of exercise restriction

Fig. 4. Echocardiogram of the same dog of Fig. 3. Heartworms are visualized as double, linear parallel objects (arrow) floating into the lumen of the right pulmonary artery.
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Symptomatic therapy includes drugs and measures that can improve cardiopulmonary circulation and lung inflation in order to relief symptoms in dogs that cannot undergo causal therapy or to prepare them for a adulticide or surgical therapy.

Restriction of exercise and, in selected cases, cage rest seems to be the most important measure to improve cardiopulmonary circulation and to reduce pulmonary hypertension (Dillon et al., 1995).

Anti-inflammatory doses of glucocorticosteroid (prednisolone 2 mg/kg s.i.d. for four or five days) given at diminishing rate can control pulmonary inflammation and thromboembolism.

Diuretics (furosemide 1 mg/kg b.i.d.) are useful when right congestive heart failure is present to reduce fluid effusions. Digoxin may be administered only to control atrial fibrillation. The use of aspirin is debatable and as not secure proofs of beneficial antithrombotic effect have been reported, for this reason the empiric use of aspirin is not advised (Knight, 1995).

The organical arsenical melarsomine dihydrochloride is the only available compound to be used in the adulticide heartworm therapy in dogs.

Two intramuscular injections of 2.5 mg/kg 24 hours apart is the standard regimen, but to reduce the risk of pulmonary thromboembolism a more gradual two step treatment is strongly advised by giving one injection and then administering the standard pair of injections at least 50 days later (Keister et al., 1992; Rawlings and McCall, 1996). In fact, one administration of melarsomine at the dose of 2.5 mg/kg kills about 90% of male worms and 10% of female worms resulting therefore in 50% reduction of the worm burden (which is safer in terms of embolism and shock). For this reasons, the three-injection alternative protocol is the treatment of choice of the American Heartworm Society and several university teaching hospitals, regardless of stage of disease.

Pulmonary thromboembolism is an inevitable consequence of a successful adulticide therapy. If several worms die widespread pulmonary thrombosis frequently develops. Mild thromboembolism may be clinically unapparent, but in severe cases life threatening respiratory distress can occur.

These complication can be reduced by restriction of exercise (no walks, no running around; the dog must stay indoors or, in selected cases, a cage rest) during the 30-40 days following the treatment and by administration of calcium heparin and anti-inflammatory doses of glucocorticosteroid to control clinical signs of thromboembolism (Di Sacco and Vezzoni, 1992; Vezzoni et al., 1992; Rawlings and McCall, 1996).

It is now known that certain macrocyclic lactones have adulticidal properties (McCall et al., 2001).

Experimental studies have shown ivermectin to have partial adulticidal properties when used continuously for at least 16 months at preventative doses (6-12 mcg/kg/month) and 100% adulticidal efficacy if administered continuously for over 30 months (McCall et al., 2001).

While there may be a role for this therapeutic strategy in few and selected cases in which patient age, or concurrent medical problems prohibit melarsomine therapy, the current recommen-
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dations are that ivermectin is not adapted as the primary adulticidal approach, and that this kind of therapy should be used carefully. In fact, the adulticide effect of ivermectin generally requires long time span before heartworms are eliminated completely. Furthermore, the older are worms when first exposed to ivermectin, the slower they are to die. In the meantime, the infection persists and continues to cause disease. Clinical observations suggest that heartworm-positive active dogs in prolonged ivermectin treatment may worsen if ivermectin is given monthly for 2 years (Venco et al., 2004).

Surgical therapy is advised when several worm displacement in the right cardiac chambers produces the sudden onset of severe symptoms (caval syndrome). It can be accomplished under general anaesthesia with Flexible Alligator Forceps introduced via jugular vein.

Flexible Alligator Forceps aided by fluoroscopic guidance can access not only right cardiac chambers but also pulmonary arteries. The main pulmonary artery and lobar branches can be accessed with flexible alligator forceps, aided by fluoroscopic guidance (Ishihara et al., 1990). Intra-operative mortality with this technique is very low. Overall, survival and rate of recovery of dogs at high risk of pulmonary thromboembolism is improved significantly by physically removing as many worms as possible. When the facilities are available, worm extraction is the procedure of choice for the most heavily infected and high risk dogs. Before electing this method of treatment, echocardiographic visualization of the pulmonary arteries should be performed to determine if a sufficient number of worms are in accessible locations.

Surgical removal of heartworm can avoid pulmonary thromboembolism, as compared to pharmacologic adulticides, such as melarsomine (Morini et al., 1998). This procedure, however, requires specialized training and instrumentation, including fluoroscopic imaging capabilities. Nevertheless, it remains a very good and a safe alternative for the management of high risk patients and the best choice in dogs harbouring a large worm burden.

References


