

# Feline Heartworm Disease

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## Introduction

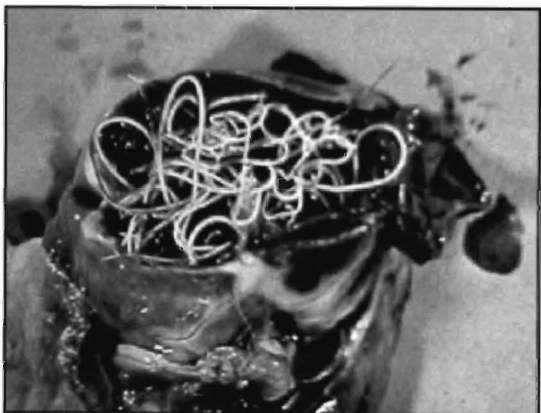
*Dirofilaria immitis* is the etiologic agent for canine heartworm disease. Although it is most notably associated with disease in dogs, various other species can serve as the definitive hosts. When left unchecked, infection can be fatal. Heartworm disease in cats is an interesting and sometimes frustrating condition to deal with as it is difficult to diagnose. The true prevalence of this disease in felines is unknown. It is believed to be less than that in dogs in the same endemic areas. This paper is intended to review heartworm disease as it relates to cats with respect to prevalence, clinical signs, diagnosis, and treatment.

*Dirofilaria immitis* has a complicated life cycle involving two hosts. The cycle starts when a mosquito, the intermediate host, takes a blood meal from an infected definitive host animal. The mosquito ingests microfilariae, the first-stage larvae (L1), with the blood meal. These microfilariae undergo two molts over 2 to 2.5 weeks within the mosquito's gut to develop into third-stage larvae (L3), the infective form of *D. immitis*. A functional adult infection cannot develop in the host without this stage of the life cycle. For this reason, microfilariae passed to a host animal through blood transfusions or via the placenta do not develop into adult heartworms. The L3 larvae are carried in the mosquito's saliva and are passed into the host animal when a blood meal is taken. The L3 larvae then travel in the subcutis of the host animal and molt into the L4 larval stage in approximately 9 to 12 days. The larvae then further molt into the L5 larval or adult stage. It is this stage that begins to migrate into the vascular system approximately 100 days post-infection.

Once in the circulatory system, the L5 larvae travel to the peripheral pulmonary arteries of the caudal lung lobes. It usually takes a minimum of five to six months before an infection becomes patent (when the gravid female worms release their microfilariae).<sup>1</sup>

## Differences Between Cat and Dog Heartworm Disease

Cats and dogs differ in rate of, and response to, infection. Cats are susceptible definitive hosts, but are more resistant than dogs. An increased exposure to infected mosquitoes carrying L3 larvae is required for cats to develop the disease, and some cats remain immune to infection.<sup>2</sup> It is not known why dogs make a better definitive hosts than cats. Some suggestions include that cats are biologically less hospitable hosts than dogs, or that the various species of mosquitoes transmitting heartworm do not bite cats as often as dogs.<sup>3</sup> Adult worms do not live as long in cats (two to three years) as they do in dogs (seven years), and the adult worms are usually smaller in cats than in dogs. The average prepatent period is longer in cats (eight months) than in dogs, as mentioned earlier (five to six months). Microfilaremia in infected cats is usually low and transient in nature with less than 20% of naturally infected cats having detectable microfilaria.<sup>4</sup>



Adult *Dirofilaria immitis* present in the right atrium of a feline heart.

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Feline heartworm disease has been recognized in many countries. Within the United States, cases of canine and feline heartworm infection are generally considered to be most prevalent in the southeastern states and along the Mississippi River. A retrospective survey of feline heartworm cases in the United States was conducted with feline and canine case records from the Veterinary Medical Data Base program at Purdue University from the years 1964-1994. In general, the results indicated that heartworm infection occurs in cats in the same geographic areas that it occurs in dogs, but at a much lower rate of only 5-20% of that seen in dogs.<sup>5</sup> In this study, feline heartworm disease was reported in 29 of the 50 states. The cases involved were referral cases presented to universities from private practitioners and all cats had severe clinical illnesses at the time of presentation. It is possible that the prevalence rates of disease in cats could be higher as many cases of feline heartworm may be misdiagnosed or infections may be subclinical. Whatever the situation may be, cats are not infected as often as dogs since they do not appear to be as suitable a host. Any age of cat is susceptible to infection but younger male cats (three to six years old) and stray cats are more likely to be infected as they tend to spend a greater amount of time outdoors. However, strictly indoor cats may also be infected.

### **Pathophysiology**

The pathophysiology of heartworm disease is similar in cats and dogs. Pathologic changes begin to occur within days after the adult worms travel to and enter the caudal pulmonary arteries. Villous myointimal proliferation of the pulmonary arteries containing adult worms is the pathognomonic lesion. This lesion develops as the adult worms cause endothelial cell swelling and an increase in width of the intercellular junctions leading to increased endothelial permeability. As a consequence the endothelium begins to slough. Activated leukocytes and platelets begin to adhere to the vessels, and release trophic factors. These factors cause smooth muscle cells within the media layer to migrate into and proliferate

in the intimal layer of the arteries. This process occurs within three to four weeks after arrival of the adult worms. The hypertrophy of the pulmonary arteries with smooth muscle, collagen, and endothelium, combined with adult worms causes the arterial lumens to narrow. This in turn leads to increased resistance to pulmonary blood flow which results in decreased vascular perfusion of the lung lobes causing partial or complete lobar consolidation, an increased pulmonary arterial pressure, and increased strain on the right heart. In cats the adult worms are more likely to cause pulmonary artery obstruction, while in dogs the villous proliferation obstructs the pulmonary artery.<sup>1</sup>

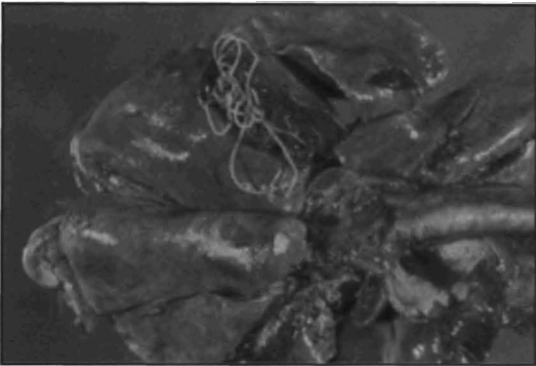
As the villous proliferation increases in the pulmonary arteries (mainly the caudal and accessory lung lobes), the pulmonary arteries start to appear blunted instead of tapered on radiographs. This may result in vessel aneurysms and peripheral occlusions. As the pulmonary arteries become occluded, there is an increase in vascular resistance which requires an increased pulmonary systolic blood pressure to perfuse the lung. This in time leads to right ventricular dilation and hypertrophy, and chronic pulmonary hypertension. Right ventricular myocardial failure and congestive heart failure may develop.<sup>1</sup>

The pulmonary arterial endothelium may suffer damage due to inflammation. Inflammatory mediators can cause local tissue destruction which results in an increase in permeability of the vessels. This leads to a periarterial edema developing in the lungs seen on thoracic radiographs as interstitial and alveolar infiltrates. These infiltrates result in areas of pulmonary consolidation.<sup>1</sup>

A final pathologic cause of pulmonary disease is due to thromboemboli of adult heartworms, alive or dead. With time, or with adulticide therapy, the adult heartworms die and degenerate. Fragments of the worms travel as thromboemboli in the vasculature and lead to occlusion of the vessels. These fragments can also cause initiation of the clotting cascade which leads to further endothelial damage. Thrombi formation also results in obstruction to blood flow, an increase in pulmonary arterial resistance, partial lung consolidation, and hy-

poxia of the alveoli.<sup>1</sup>

In cats, an alveolar type II cell hyperplasia is sometimes present in the lungs in response to dead adult heartworms.<sup>6,7</sup> Type II alveolar cells produce surfactant and normally replace type I alveolar cells when they become damaged. Many cats experience acute respiratory distress at four to nine months post-infection which may be caused by this hyperplasia or the increased incidence of pulmonary thromboembolism cats exhibit. The respiratory problems are often misdiagnosed as feline asthma. It is not known at this time if the type II hyperplasia is reversible, nor why some cats go into remission and eventually recover from their pulmonary problems and others die acutely.<sup>6</sup>



Adult heartworms in the pulmonary arteries incite a local inflammatory reaction leading to thromboembolism.

Aberrant migration of *Dirofilaria immitis* L4 larvae is more common in cats than in dogs. Adult heartworms have been found in the lateral ventricles of the brain,<sup>1</sup> subcutaneous nodules, eyes, and body cavities.<sup>4</sup> One explanation for this migration may be that as cats are not the normal definitive host for heartworms, the infective larvae become poorly oriented once inside the feline body.<sup>8</sup>

### Clinical Signs

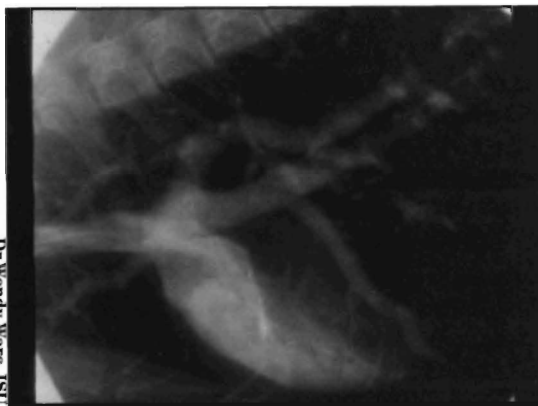
The onset of clinical signs seen with heartworm infection and the severity of the disease is related to the number of adult worms present in the animal, as well as the inflammatory response and pulmonary vessel reactivity. When only a few worms are present, they will typically remain in the caudal pulmonary arteries. As the worm burden increases the worms tend to migrate toward

the heart. Where dogs may have greater than fifty adult worms, infected cats usually have less than eight worms in the pulmonary arteries and right ventricle of the heart.<sup>1</sup> Cats tend to have more of an intense immune and inflammatory response to the adult worms, which may be why fewer adult heartworms are found in cats and why their lifespans tend to be shorter. It may also explain why infections in cats sometimes tend to be self-limiting.<sup>3</sup>

Clinical signs of heartworm disease begin to appear three to seven months post-infection and differ between cats and dogs. Signs are usually seen from late summer to early winter depending on the geographic region of the country. Dogs have fairly typical signs of coughing, dyspnea, hemoptysis, and right heart failure. In cats the signs are variable and often vague. Common clinical signs seen in acute feline cases are dyspnea, collapse, convulsions, vomiting, diarrhea, tachycardia, or syncope. In chronic cases signs include coughing, vomiting, dyspnea, lethargy, anorexia, weight loss, or chylothorax.<sup>3</sup> Some cats may be asymptomatic and then die suddenly. Others may show signs for a short while and then appear to recover.<sup>2</sup> Caval syndrome, a severe and life-threatening form of heartworm infection with heavy adult worm burdens in the vena cavae and right atrium is most commonly seen in male dogs while rarely seen in cats. Sometimes there is a sudden onset of neurologic signs including seizures, dementia, blindness, ataxia, circling, mydriasis, and hypersalivation that develop in response to aberrant worm migration.<sup>1</sup> In general, the most common signs seen in cats are dyspnea, coughing, and vomiting. Any cat with a history of chronic vomiting should have heartworm disease as a differential diagnosis.<sup>2</sup>

### Diagnosis

Diagnosis of heartworm disease is difficult and frustrating in cats. As mentioned above, clinical signs are vague and of little help in providing a diagnosis. Common blood laboratory abnormalities include an eosinophilia found in one-third of infected cats. This may lead to an incorrect diagnosis of feline asthma or lungworm infection. A mild



**Angiogram demonstrating blunting and tortuous pulmonary arteries seen with feline heartworm disease. Heartworms are seen as negative filling defects located within opacified arterial branches.**

nonregenerative anemia, basophilia, nucleated red blood cells, and hyperglobulinemia may also be seen. With advanced heartworm disease, leukocytosis with neutrophilia, a left shift and monocytosis may be present. Thrombocytopenia and disseminated intravascular coagulation may occur with pulmonary thromboemboli. Transtracheal washings usually show a microbiologically sterile eosinophilia with cytology early in the disease. Later in the disease course cytology of transtracheal washings typically result in nonspecific inflammatory cells or is unremarkable.<sup>1</sup>

Thoracic radiography is the diagnostic method of choice with feline heartworm disease. Enlargement and tortuosity of the central and peripheral pulmonary arteries on ventrodorsal radiographs, especially in the caudal lung lobes, is the most characteristic radiographic finding.<sup>9,10</sup> The increase in pulmonary arterial size is related to the duration of the heartworm infection and not to the total heartworm burden.<sup>9</sup> Main pulmonary artery segment enlargement is not a classic sign in advanced feline heartworm cases as it is in canine cases and contrast angiography is necessary to visualize it in cats as it is located more medial to the cardiac silhouette.<sup>10</sup> Cardiomegaly may be present, but it is not a consistent finding, which may indicate that it is not present until late in the course of the disease. In general, pulmonary veins are not enlarged. This finding may help to distinguish feline heartworm disease from feline dilated or hypertrophic cardiomyopathy where enlarge-

ment of the cardiac silhouette and both the pulmonary arteries and veins is usually seen.<sup>9</sup> In the lungs, diffuse or focal pulmonary densities (alveolar or interstitial lung patterns) may be seen perivascularly, and may be due to atelectasis or alveolar disease.<sup>1</sup> Thoracic radiography is a good screening method for heartworm disease and is also useful in judging the severity of the infection.

Angiography is useful in visualizing the gross morphology of the pulmonary arteries and the main pulmonary artery segment. Heartworms are seen as negative filling defects located within opacified arterial branches. Angiograms are seldom necessary however to diagnose heartworm infection.<sup>6</sup>

Echocardiography is useful to confirm a tentative diagnosis of heartworm disease if heartworms are seen in the heart or proximal pulmonary arteries. It is less useful as a screening test for diagnosis. Echocardiography is thought to be more useful in cats than dogs because the large size of the worm in comparison to the host makes it more noticeable.<sup>11</sup> Ultrasound visualization of heartworms definitively diagnoses infection, however ultrasound is limited in that it cannot visualize worms in the extremities of the pulmonary arteries where they are most likely to be found.<sup>6</sup>

Electrocardiogram results are often normal in cases of heartworm disease. Arrhythmias are uncommon with heartworm infection, but ventricular tachycardia may be seen with advanced pulmonary arterial disease or congestive heart failure secondary to heartworm disease.<sup>1</sup>

Serologic methods of diagnosis offer unique challenges in cats when compared to dogs. The microfilarial concentration tests used in dogs (modified Knott's test, millipore filter test) lyse erythrocytes and fix any microfilariae present. Cats usually have negative concentration test results as they lack microfilariae (occult infection). The amicrofilaremia may be due to low numbers or the absence of circulating microfilariae, only a brief period of time when the microfilariae are circulating, low adult worm burdens that produce few microfilariae, unisexual worm infection, or an increased immune response that rapidly kills the microfilariae.<sup>1,3</sup> Five milliliters of blood should be used for

concentration tests in cats instead of the usual one milliliter used in dogs to improve test results.<sup>10</sup>

Serologic antigen enzyme-linked immunosorbent assay tests (ELISA) are the most useful of the serologic tests in cats. These tests detect protein antigens released from adult heartworms using monoclonal culture-produced antibodies to the antigen. These ELISA tests are useful since they do not require the presence of microfilariae and do not depend on the host immune response as ELISA antibody detection tests do. The antigen tests can be used with the serum from any host species.<sup>10</sup> The specificity of antigen tests is almost 100%, but the sensitivity varies with the number and longevity of the heartworms. Unisex infections with male heartworms or immature females may give false negative test results without antigen present. These tests are semi-quantitative which gives some idea to the number of heartworms present based on the quantity of antigen produced.<sup>3</sup> No current antigen test can detect infection before five months in infected cats.<sup>11</sup>

ELISA tests for host antibody are useful diagnostic methods, and should be run in conjunction with antigen tests. These tests are more sensitive for heartworm infection, but lack the specificity of antigen tests. False positive test results may occur with the host producing antibody in response to precardiac heartworm larvae that never fully develop. Negative test results are a good indication that a cat is not currently infected.<sup>6</sup>

A final method of diagnosis for feline heartworm disease is necropsy. This is where asymptomatic cases that end in sudden death are often found. Necropsies should be performed on all suspect heartworm cases or with any case that ended in an unexplained death. One must perform a thorough search of the pulmonary arteries, right side of the heart, and the systemic veins since one or two worms may be all that are present. In addition the worms may be difficult to find if they are dead and fragmented, or in the extremities of the pulmonary arteries. Heartworms in cats may also be present in ectopic sites through aberrant migration so the systemic arteries, body cavities, and the central nervous system (if neurologic signs are present) should be examined.<sup>6</sup>

## Treatment

The efficacy of treatment of heartworm disease differs between cats and dogs. The common protocol in dogs, known to be infected with heartworms, involves using adulticide therapy followed by microfilaricide treatment and finally, using prophylactic medication. In cats, severe complications may result that are more serious than the initial disease. It is generally recommended to allow heartworm disease to run its course in asymptomatic cats. These cats may recover spontaneously, and as infected cats appear to be dead-end hosts (or amicrofilaremic); the risk of infection of other animals in the environment is low. The possibility of spontaneous thromboembolism and sudden death resulting from lack of treatment must always be considered.<sup>10</sup> Subclinical cases of heartworm disease should be monitored every six months with thoracic radiographs.<sup>6</sup>

Adulticide therapy is warranted in cats with overt clinical signs. The rare cases of caval syndrome should be treated immediately with surgical removal of the adult worms.<sup>6</sup> The adulticide treatment of choice is sodium thiacetarsamide (2.2 mg/kg IV twice daily for two days), the same dosage used in dogs. There are many complications that may develop in cats in response to this therapy and owners should be informed of the risks ahead of time. Sodium thiacetarsamide is eliminated by cats more slowly than in dogs, so the possibility of toxicity occurring is greater. Young female worms are the most resistant to this drug, so multiple treatments may be necessary, causing drug concentrations to accumulate quickly in cats.

Complications from treatment include tissue sloughing if extravasation of the caustic arsenic drug accidentally occurs. Edema due to arteriolar dilation and loss of capillary integrity may result in protein loss, anorexia, profound depression, nausea, vomiting, and severe pulmonary thromboembolism of the dead worm fragments.<sup>1</sup> Melarsamine is currently being investigated for use in cats, but at present, it is not utilized in this species.

Thromboembolic disease is the most serious consequence of adulticide therapy which can result in sudden death. This commonly

occurs 5 to 14 days after the first treatment and may be seen up to four weeks later. Common clinical signs include fever, cough, dyspnea, hemoptysis, pallor, pulmonary crackles, tachycardia, and hypotension. Treatment involves aminophylline (a bronchodilator) and anti-inflammatory doses of glucocorticoids. Intravenous fluids and oxygen therapy may be given as needed.<sup>1</sup>

Aspirin and microfilaricide therapy in cats is generally not recommended unless pulmonary thromboembolism is already present. Aspirin therapy may be used in conjunction with adulticide therapy in dogs to reduce platelet aggregation leading to increased thromboemboli and pulmonary hypertension. In cats the effects of aspirin do not appear to help significantly and the therapeutic dose necessary is near the toxic dose, so aspirin should be avoided.<sup>12</sup> Because most cats have occult heartworm infections, microfilaricides (ivermectin, dithiazanine, or levamisole) are usually unnecessary.<sup>1</sup>

### Prevention

Preventive therapy may be considered for cats in known endemic areas for *Dirofilaria immitis* although the incidence of infection is not high. Ivermectin has been proven efficacious, and in 1997, it was approved for use in cats as a prophylactic medication for heartworms. The dose is 24 micrograms per kilogram body weight given once a month throughout the mosquito season.<sup>6,13</sup> Monthly doses of milbemycin oxime or daily doses of diethylcarbazine at the recommended canine doses can be given, but are generally not recommended.<sup>6</sup>

### Conclusion

Cats can become infected with heartworm disease although the prevalence is not high. Diagnosis and treatment of the clinical disease can be unrewarding. There is still much research to be done to better understand the course of the disease in cats and to improve treatment options. Preventive therapy is up to the private practitioner's discretion, but it should be considered in endemic areas. This paper has hopefully given an overview on an interesting feline disease that is becoming increasingly diagnosed in this species. ♦

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