Canine and Feline Dirofilariasis: Life Cycle, Pathophysiology, and Diagnosis*

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ABSTRACT: Infection with the intravascular parasite *Dirofilaria immitis* is an increasingly recognized problem in domestic dogs and cats. Heartworm infection is preventable; however, once an animal is infected, heartworm disease and potentially life-threatening complications can develop. An understanding of the heartworm life cycle and transmission season, the limitations of testing methods, and the clinical signs of heartworm disease is necessary to provide clients with appropriate information regarding prevention and treatment of heartworm infection in their pets.

Dirofilaria immitis infects a wide variety of animal species, including domestic dogs, wolves, foxes, coyotes, domestic cats, ferrets, muskrats, sea lions, nondomestic cats, coatimundi, and humans.[1] The distribution of heartworm infection is mainly determined by the distribution of canine reservoir species (Figure 1). Heartworm infection can be prevented in domestic dogs and cats by regular administration of parasiticide agents.

CANINE HEARTWORM DISEASE
Life Cycle

Understanding the complex life cycle of *D. immitis* is crucial to making appropriate recommendations about testing for and treating heartworm infection. The heartworm life cycle has five larval stages (L1 through L5; Figure 2). Adult heartworms typically live in the pulmonary arteries but may invade the right ventricle, right atrium, and caudal vena cava in heavy infections. After mating, the female worms release microfilariae (L1) into the host's bloodstream, where they can be ingested by feeding mosquitoes. While in the mosquito, the larvae will molt twice (L1 to L2 to L3) over an 8- to 17-day period. The time required for these molts to occur is temperature dependent. If the ambient temperature is not adequate (i.e., at least 57°F [14°C]) for a sufficient number of days during the lifetime of an infected vector mosquito, transformation to the L3 stage does not occur.[1]

The L3 stage—the infective stage of the heartworm—is transmitted to a new host when the vector mosquito feeds. The L3 larvae molt

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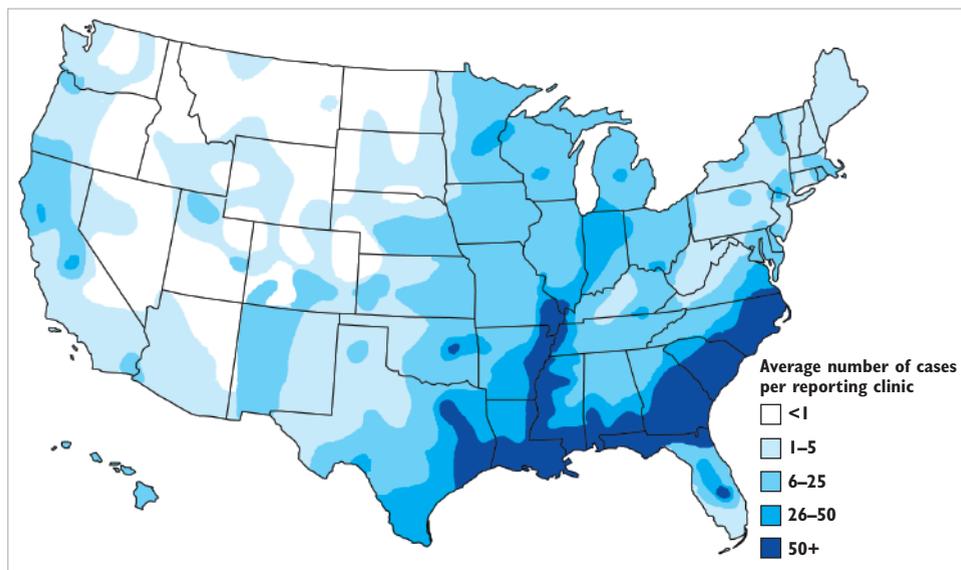- See full-text articles

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Figure 1. Canine heartworm incidence in the United States, based on the average number of cases per reporting clinic, in 2005. Some remote regions of the country lack veterinary clinics; therefore, there are no reported cases from these areas. (© American Heartworm Society, 2005)

signs of respiratory disease.[1] The adult worms typically live in the caudal pulmonary vascular tree, where they cause further damage through the release of toxic substances, the host's own immunologic reaction to these substances, and physical trauma. The initial vascular changes include endothelial damage and sloughing, villous proliferation, and activation and attraction of leukocytes and platelets. These changes may eventually lead to smooth muscle cell proliferation and collagen accumulation, resulting in fibrosis. Dead or dying worms cause the most severe damage, including thrombosis, granulomatous inflammation, and rugose, villous inflammation. Affected vessels may become thrombosed, thickened, dilated, tortuous, noncompliant, and functionally incompetent.

Heartworms release vasoactive substances that result in vasoconstriction and hypoxia, which lead to pulmonary hypertension and compromised cardiac output.[2] Pulmonary hypertension causes pressure overload of the right ventricle, resulting in compensatory, concentric ventricular hypertrophy (thickening of the ventricular walls). In severe cases (high worm burdens or chronic infections), chronic pulmonary hypertension with tricuspid insufficiency results in elevated cardiac filling pressures and congestive heart failure. Thromboembolism may cause acute decompensation by producing or aggravating pulmonary hypertension, right heart failure, or pulmonary infarction. Therefore, dead worms tend to worsen the vascular damage and enhance coagulation.

The pulmonary parenchyma can also be damaged. Eosinophilic pneumonitis is the most commonly reported parenchymal lesion and is caused by immune-mediated destruction of microfilariae within the pulmonary vasculature and the subsequent inflammatory reaction.[3] Much less commonly reported is pulmonary eosinophilic granulomatosis, which develops when microfilariae trapped within the lungs are surrounded by neutrophils and eosinophils, leading to granuloma formation. The most severe manifestation of heartworm

to the L4 stage in the host's subcutaneous, adipose, or skeletal muscular tissue 1 to 12 days after infection. The final molt from the L4 stage to the L5 immature adult occurs 50 to 68 days after the initial infection. The immature adults enter the vascular system and migrate to the heart and pulmonary arteries, where they mature into adult heartworms over the next 99 to 152 days. Adult male heartworms can grow to be 6 to 7 inches (15 to 18 cm) in length; adult females can reach 10 to 12 inches (25 to 30 cm). Under ideal conditions, the entire life cycle (microfilaria to mature adult) takes 184 to 210 days. Because only mature adults are capable of reproduction, dogs do not typically become microfilaremic for 6 to 8 months after initial infection. Adult heartworms typically live for up to 5 years in dogs. Microfilariae may live as long as 30 months.[1]

Pathophysiology

The primary damage in heartworm infection occurs in the pulmonary arteries and lungs. The degree of damage depends on the number of worms present, the duration of infection, and the host's reaction to the parasites' presence. It is believed that the L5 heartworms cause the damage when they reach the pulmonary artery (3 months after infection).[1] The immature adult worms initiate vascular damage and possibly lung disease by causing eosinophilia with eosinophilic infiltrates and
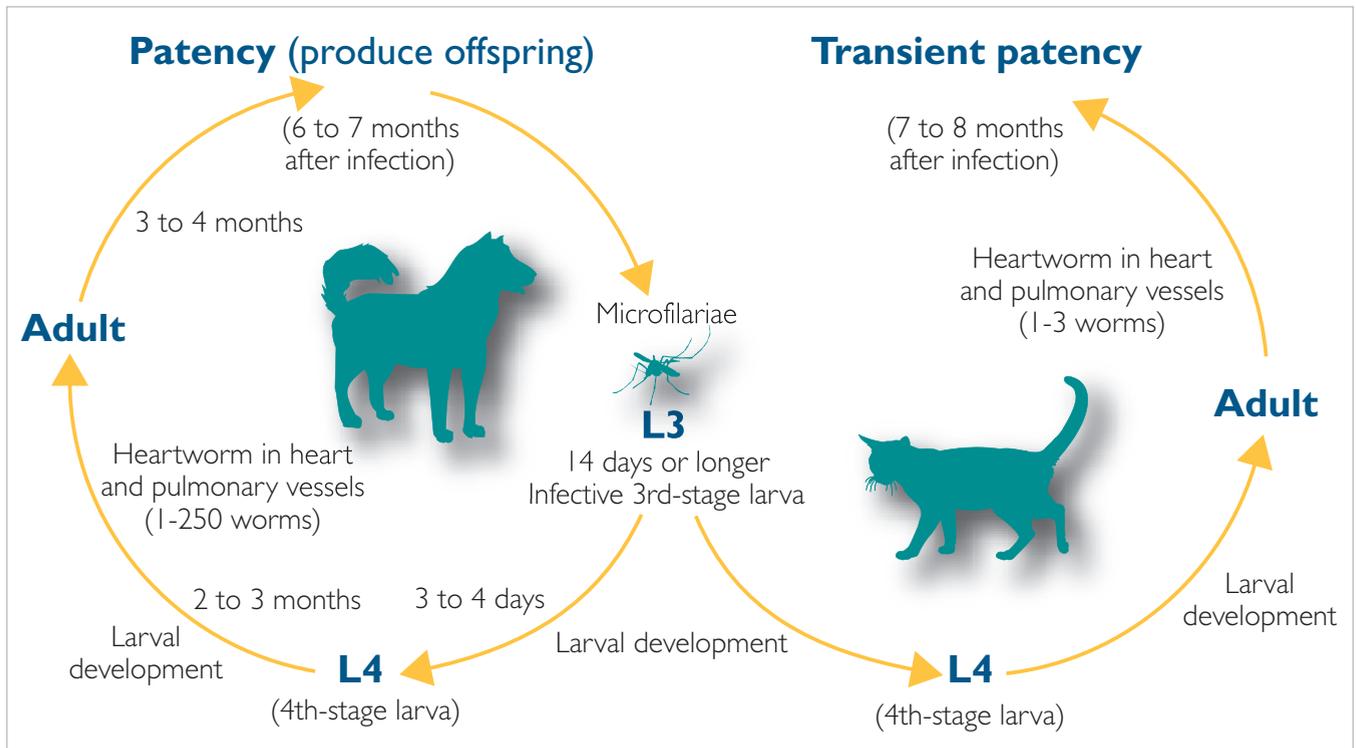
Figure 2. *Dirofilaria immitis* **life cycle in dogs and cats.** (© American Heartworm Society, 2007)

disease is caval syndrome, in which a percentage of the worm burden is redistributed to the right ventricular inflow tract, resulting in severe tricuspid regurgitation and decreased forward flow. Hemolytic anemia, secondary to traumatic destruction of the red blood cells as they pass through the worm mass, also occurs. This intravascular hemolysis leads to hemoglobinuria.[4] Some patients with caval syndrome present with clinical signs referable to right-sided congestive heart failure.

Heartworm infection may also lead to glomerulonephritis and proteinuria secondary to antigen–antibody complex formation. However, this does not commonly lead to renal failure.[5] Heartworms can also produce disease by means of aberrant migration in tissues such as the brain, spinal cord, eye, liver, or skin. The resulting lesions depend on the path of migration.

Clinical Signs

Most dogs with heartworm infection have no clinical signs, regardless of worm burden and duration of infection. In these animals, infection is often an incidental finding on routine screening. Only dogs with very high worm burdens or complications of heartworm infection present to the hospital with clinical signs of heartworm disease. Heartworm disease is the clinicopathologic manifestation of heartworm infestation of the pulmonary arteries, right side of the heart, and vena cava and may include pneumonitis, pulmonary endarteritis, pulmonary hypertension, pulmonary thromboembolism, and cor pulmonale.

The observed clinical signs depend on the severity of disease (pathology caused by the worms and vasoactive substances) and the duration of infection. They often reflect the effects of the parasites' presence in the pulmonary arteries and lungs. The history may include weight loss, diminished exercise tolerance, lethargy, poor body condition, cough, dyspnea, syncope, and abdominal distention/ascites.[1] If severe heartworm disease with pulmonary hypertension is present, physical examination may reveal a split second heart sound, a right-sided heart murmur (tricuspid insufficiency), and a cardiac gallop.[6] Cardiac arrhythmias and conduction disturbances are uncommon. In severe cases, premature atrial and ventricular beats can be present. Jugular venous distention or pulse, hepatosplenomegaly, and ascites may be present in patients with right-sided congestive heart failure. Pulmonary signs include crackles, cough, dyspnea, cyanosis, and hemoptysis.[1]

Diagnosis
Laboratory Tests

Heartworm infection can be diagnosed on routine screening before the development of clinical signs by directly examining the blood for microfilariae or by testing for the presence of circulating antigens in the blood, serum, or plasma.

Antigen testing using an ELISA is the preferred method of heartworm diagnosis. These tests are easy to use, highly sensitive, and highly specific. However, these tests produce false-negative results during the first 5 to 8 months of infection, in animals infected with only male worms, and in animals infected with few female worms. Some ELISAs are designed to quantify the worm burden based on the concentration of antigen produced by the mature female worm, but they may also produce inaccurate results if most of the worms are male or if antigen levels are elevated due to worm death.[1] The local prevalence of heartworm disease affects the positive and negative predictive values of the ELISA. The positive predictive value of this test in populations with a high incidence of heartworm infection is superior to that in populations in which the incidence is low. For this reason, it is important for veterinarians to know the prevalence of heartworm infection in their local practice area to better interpret the results of an ELISA.

Examination of a direct smear may detect microfilariae and may help to distinguish *D. immitis* from *Acanthocheilonema reconditum* (previously called *Dipetalonema reconditum*). False-negative results may be obtained if the infection is occult (amicrofilaremia), the number of circulating microfilariae is low, or an insufficient amount of blood is examined. Animals may be amicrofilaremic for a number of reasons, including previous administration of heartworm preventative, single-sex infections, prepatent infections, and immune-mediated destruction of the microfilariae. Methods that concentrate the microfilariae for detection include the microhematocrit tube evaluation (above the buffy coat), modified Knotts test, and millipore filtration test. A test to detect microfilariae should always be conducted in antigen-positive animals.[1] The modified Knotts test and the millipore filtration test
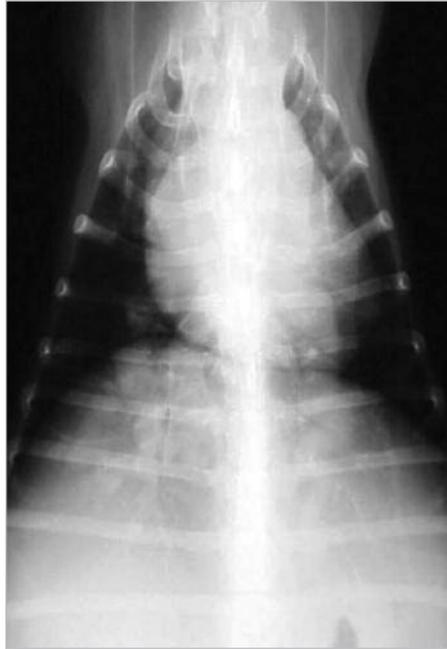

Figure 3. Dorsoventral radiograph of a patient with heartworm disease, revealing right-sided heart enlargement.

are superior to the evaluation of the microhematocrit tube.[1]

Radiography

Thoracic radiographs alone are not diagnostic for heartworm infection but are useful for detecting heartworm disease, determining disease severity, and evaluating cardiopulmonary parenchymal changes. Radiographic changes associated with heartworm disease include right ventricular enlargement (Figure 3), increased prominence of the main pulmonary artery segments, increased size and density of the pulmonary arteries, arterial tortuosity, and pruning.[7] The size of the caudal lobar pulmonary vessels is best evaluated on the dorsoventral projection. The vessels are considered abnormal if they are larger than the diameter of the ninth rib where the rib and the artery intersect. The cranial lobar pulmonary artery is best evaluated on the left lateral projection and should not be larger than its accompanying vein or the proximal one-third of the fourth rib (Figure 4). Thoracic radiographs can also be used to evaluate the pulmonary parenchyma for infiltration, nodules, lymphadenopathy, and pleural effusion. Pulmonary parenchymal changes may include a mixed interstitial to alveolar pattern that is typically most severe in the caudal lung lobes. In eosinophilic nodular pulmonary granulomatosis, the pattern may appear nodular.[1] Radiographic changes may be transient and do not always indicate an active infection.

Echocardiography

Echocardiography is sensitive in detecting right heart dysfunction in which the right ventricular end diastolic dimension and right ventricular free wall thickness are increased (i.e., right-sided heart enlargement). In some infections, worms may be detected in the pulmonary artery and/or right heart (Figure 5). Echocardiography can be useful to estimate worm burden, the presence of tricuspid regurgitation, and the severity of pulmonary hypertension. A diagnosis of caval syndrome can be confirmed with echocardiography.[1]
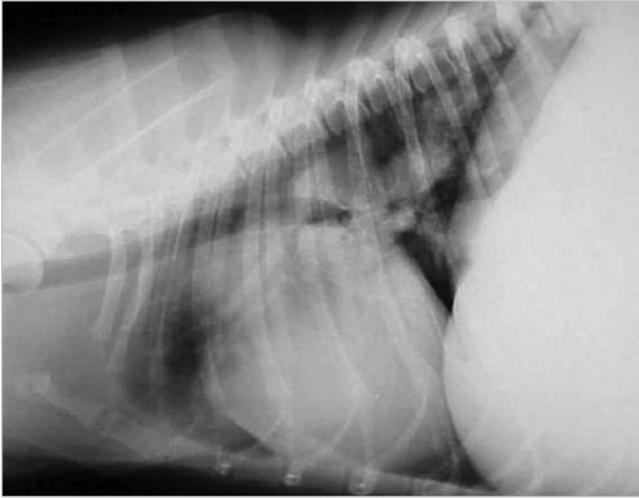
Figure 4. Lateral radiograph of a patient with heartworm disease, revealing marked pulmonary vessel enlargement.

Figure 5. Echocardiogram of a patient with heartworm disease. The presence of adult heartworms is indicated by the *arrow*.

Electrocardiography

Electrocardiography is used to detect arrhythmias but is usually less sensitive for detection of cardiac chamber enlargement than radiography and echocardiography. Electrocardiography may reveal right axis deviation[1] if moderate to severe pulmonary hypertension is present. Arrhythmias, such as premature atrial or ventricular beats, and conduction abnormalities (right bundle branch block) are uncommon unless cardiac enlargement is moderate to severe.

Clinical Pathology

Clinical pathology results are often not diagnostic for heartworms, but they are useful in evaluating for concurrent disease processes. Abnormalities identified with heartworm infection may include mild nonregenerative anemia, neutrophilia, eosinophilia, basophilia, and thrombocytopenia.[8] Liver enzyme elevations, azotemia, and hyperbilirubinemia may be noted in patients with severe heartworm disease. On urinalysis, proteinuria (albuminuria) may be noted. Tracheal wash cytology may reveal eosinophilic inflammation; microfilariae are rarely noted. If ascites is present, abdominal fluid analysis is consistent with right-sided congestive heart failure (modified transudate).[1]

FELINE HEARTWORM DISEASE

In 2007, the American Heartworm Society released new guidelines on feline heartworm infection. This publication, along with recent research into the differences between canine and feline heartworm disease, has

increased veterinarians' need to be aware of the clinical manifestations of heartworm disease in cats. Cats are inherently resistant to heartworm infection. Therefore, although the rate of feline heartworm infection correlates with that for dogs in the same geographic region, it is typically 5% to 20% of that in dogs.[9] Knowing the local rate of heartworm infection in dogs can therefore help veterinarians educate cat owners as well as dog owners about their pet's risk of infection. Debunking persistent myths about feline heartworm infection—for example, that indoor cats are not at risk—is also important in helping prevent feline heartworm disease.

Life Cycle

The life cycle of heartworms in cats is similar to that in dogs. Heartworms in cats have a much shorter life span (2 to 3 years).[10] Cats are very efficient at clearing heartworm larvae in the immature stages. Cats also appear to demonstrate immune-mediated clearance of microfilariae as well as suppression of the female heartworm's reproductive ability.

Pathophysiology

Heartworm-infected cats usually have low worm burdens (two to four worms).[10] As in dogs, immature adults may induce pulmonary vascular disease before maturation. These changes may develop in cats that resist mature infection.[9] The pulmonary arterial response to adult heartworms is more severe than that in dogs. Cats have a smaller pulmonary arterial tree with less collateral circulation, making them more susceptible to worm embolization.[9] The clinical signs associated with the presence and death of heartworms within the pulmonary arteries in cats have become part of a syndrome known as *heartworm-associated respiratory disease*. Rarely, heartworm infection in cats may lead to right heart failure, resulting in pleural (may be chylous) effusion, ascites, or both.

Clinical Signs

Many cats with heartworm infection show no clinical signs. When present, clinical signs may be peracute, acute, or chronic. Acute or peracute signs are often due to worm embolization or aberrant migration, which is more common in cats than in dogs. These signs may include cough (38%), salivation, tachycardia, shock, dyspnea (48%), hemoptysis, vomiting and diarrhea, syncope, dementia, ataxia, circling, head tilt, blindness, seizures, and death (10%).[11] Chronic signs are more common and include anorexia, weight loss, lethargy, exercise intolerance, right

heart failure, coughing, dyspnea, and vomiting. Murmurs are not commonly associated with feline heartworm disease because caval syndrome and right-sided cardiomegaly with subsequent valvular insufficiency are rare in cats.

Diagnosis

The diagnosis of heartworm infection and disease in cats may be difficult. The clinical signs exhibited by cats with heartworm infection or disease are much different than those exhibited by dogs. Additionally, cats are naturally resistant to heartworms; therefore, the index of suspension is often low, based on the clinical signs present. Diagnosis is difficult because cats often have a very low worm burden or a single-sex male infection. For this reason, antigen tests are not always useful in detecting heartworm infection in cats. Antibody detection is another option but does not always correlate with an active infection and indicates exposure only. A cat that cleared the L5-stage larvae before they matured will be antibody positive.

Thoracic radiography may be helpful in making a diagnosis, but as in dogs, the changes seen on radiographs may be transient and may not indicate an active infection. A cat with an active heartworm infection may have normal radiographs or enlarged pulmonary arteries, particularly the caudal lobar arteries. Echocardiography seems to be the most sensitive diagnostic test, detecting heartworm infection in 78% of cases.[12] Due to the small size of cats, heartworms can often be seen in the main pulmonary artery as double parallel hyperechoic lines within the vessel. However, it is difficult to determine the number of worms because the worms may be tortuous and the image produced may show multiple sections of the same worm.

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1. Which of the following is the preferred diagnostic test for detection of heartworm infection in dogs?
   a. thoracic radiography
   b. echocardiography
   c. antigen test
   d. detection of microfilariae

2. Antigen tests may produce false-negative results in animals infected with
   a. only male worms.
   b. few female worms.
   c. a and b
   d. none of the above

3. Which statement regarding testing for heartworms in cats is false?
   a. A positive antibody test indicates exposure to heartworms.
   b. A positive antibody test confirms the diagnosis of heartworm infection.
   c. A negative antigen test does not rule out heartworm infection.
   d. Echocardiography may be required for the diagnosis of heartworm infection.

4. The infective stage of heartworms is the _____ stage.
   a. L1
   b. L2
   c. L3
   d. L4

5. In dogs, the pulmonary vessels are evaluated where the artery intersects the _____ rib in the dorsoventral radiographic view.
   a. sixth
   b. seventh
   c. eighth
   d. ninth

6. In the lateral radiographic view, the arteries in dogs are compared with the accompanying vein or the proximal one-third of the _____ rib.
   a. second
   b. third
   c. fourth
   d. fifth

7. The presence of adult heartworms in the pulmonary arteries results in
   a. villous proliferation of the intima and subintimal vascular smooth muscle.
   b. pulmonary hypertension secondary to obstruction of blood flow and decreased vascular compliance.
   c. vascular damage associated with direct contact of the worms with the endothelium.
   d. all of the above

8. Which of the following statements is false regarding heartworm infection in cats?
   a. The frequency of feline heartworm infection correlates with that for dogs in the same geographic region, but at a lower incidence (infection rate is 5% to 20% that in dogs).
   b. Indoor cats are not at risk.
   c. Cats have a smaller pulmonary arterial tree with less collateral circulation, making them more susceptible to worm embolization.
   d. Chylous pleural effusion in cats can be associated with heartworm disease.

9. Which of the following statements is true?
   a. The positive or negative predictive value of an ELISA is not affected by the prevalence of heartworm infection in a region.
   b. The most common pulmonary infiltrate noted with heartworm infection is macrophages.
   c. Detection of microfilariae is the most reliable method of determining the heartworm status of a patient.
   d. Occult (amicrofilaremic) infection can be associated with a prepatent infection.

10. Eosinophilic pneumonitis is
   a. due to immune-mediated destruction of adult worms in the pulmonary circulation.
   b. due to inflammation secondary to the presence of adult worms in the pulmonary circulation.
   c. due to immune-mediated destruction of microfilariae within the pulmonary circulation.
   d. not associated with heartworm disease.