Heartworm Biology, Treatment, and Control

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KEYWORDS

• *Dirofilaria* • Microfilariae • Right heart failure
• Caval syndrome • Heartworm development units

Dirofilaria immitis, the ''inexorable dreaded threadworm,'' remains the most serious parasitic disease of the dog in North America. These worms are white and approximately a foot in length; males are 12 to 20 cm long and females are 25 to 31 cm long. The worms cause severe lung pathology and morbidity in the dog, shorten the animal's life expectancy, and can cause acute disease and death. Due to the spread of heartworm disease throughout the nation, there are more dogs at risk now than there were 100 years ago. An excellent array of products is available that prevent infection when used on a regular basis. Also, treatment of infected dogs has improved markedly with the introduction of the intramuscularly delivered melarsomine dihydrochloride, but there still can be numerous difficulties and complications, especially in dogs that present after developing severe heartworm associated disease. In most parts of the United States, dogs that are not on preventive therapy are at risk of infection. There is little doubt that cats also get infected with larvae from mosquitoes, though the disease manifestations are different and more subtle than in the dog. Moreover, there have been several reports of these worms causing lesions and clinical signs in the lungs of people throughout the United States. In the United States, coyotes and the unprotected canine population provide reservoir hosts that continue to place dogs, cats, and people at risk of obtaining heartworm infections from the bites of infected mosquitoes.

BIOLOGY

Affinities

The canine heartworm, *Dirofilaria immitis*, is in the phylum Nematoda, class Secernentea, order Spirurida, suborder Spirurina, superfamily Filarioidea, family Onchocercidae, and subfamily Dirofilariinae.[1] This organization of the Nematoda that defines the affinities of the genus *Dirofilaria* based on biologic and morphologic criteria is

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supported by recent ssu RNA gene phylogenies.[2] The Onchocercidae contains some 75 or so genera that have microfilariae found in the blood or skin. By making use of biting vectors that feed on blood or skin and ingest microfilariae, the adult worms can live in tissues of the body that have no direct connections to the external environment, for example, the meninges, lymphatics, and blood vessels, rather than the intestinal tract or tracheal system.[1]

Vertebrate Final Hosts

Although known earlier in Europe, the dog heartworm was first described as a new species in the United States.[3] The worm was first reported in the United States in 1847 in a dog from Erie, Alabama that was described as having a massive number of white worms in its heart and large vessels.[4] The domestic dog, *Canis familiaris*, is the typical host of the heartworm. *Dirofilaria immitis* originated in Asia, had a long history in countries bordering the Mediterranean, and was brought to the Americas in dogs by early explorers and immigrants. At the time of the European arrival in the Americas, there were few representatives of *Canis lupus familiaris* among the Native American population, but there was an indigenous canid population represented by wolves, coyotes, and foxes.

Within the canine hosts of the Americas, heartworms have been recovered from the domestic dog, gray wolf, coyote, red fox, gray fox, maned wolf, and crab-eating fox. Around the world, other wild canids reported to be infected with heartworms include the jackal (*Canis aureus*), the raccoon dog (*Nyctereutes procyonoides*), the dhole (*Cuon alpinus*), and the African wild dog (*Lycaon pictus*).[5,6] A tabular summary of the occurrence of heartworms in the United States by state in coyotes, wolves, and gray and red foxes is presented by Anderson.[7,8] It seems that all members of the genus *Canis* can support the development of patent *D immitis* infections and serve as wildlife reservoirs.[6] The raccoon dog and the African wild dog have also been found to support patent infections with heartworms.[6] Foxes of the *Vulpes* and *Urocyon* genera are not as likely to support long-standing patent infections, and are therefore unlikely to be of major importance as reservoir hosts.[6,9] The other genera of canines have not been examined sufficiently to determine their potential role as reservoirs.[6]

Infections have been reported from hosts other than canines. Felids, both the domestic cat and several other species, can develop infections with heartworms; however, like foxes, felids tend not to serve as biologic reservoirs of the infection.[6] A recent list of hosts included feline hosts: the ocelot (*Leopardus pardalis*), mountain lion (*Felis concolor*), clouded leopard (*Neofelis neburosa*), snow leopard (*Uncia uncia*), Bengal tiger (*Panthera tigris*), and lion (*Panthera leo*).[6] Other hosts occasionally have nonpatent heartworm infections with one to several worms, and such hosts include primates, deer, beavers, muskrats, horses, wolverines, coatimundis, red pandas, raccoons, bears, seals, and sea lions; domestic ferrets can develop heartworm.[5,6,10]

Intermediate Hosts/Vectors

Members of the genus *Dirofilaria* are most commonly transmitted by mosquitoes that ingest blood containing the relatively long unsheathed microfilariae with tapered tails. However, unlike human malarias, in which only the genus *Anopheles* can serve as a vector of the important *Plasmodium* species, *Dirofilaria immitis* is capable of developing in mosquitoes from several different families. More than 60 species of mosquitoes around the world have been shown to be susceptible to infection, and 13 species collected in the field in the United States were infected with *D immitis* larvae.[9] In 1998 Scoles summarized the mosquitoes found to be naturally infected with *D immitis* (**Table 1**).[11]

Table 1
Mosquito species collected naturally infected with filariids presumed to be *Dirofilaria immitis* in the United States

Species	Locations (State)	Total Reports[a]	Number of Reports with L_3[b]
Aedes albopictus	FL, LA	3	1
Aedes canadensis	CT, FL, MA, NJ	4	4
Aedes cantator	NJ	1	1
Aedes excrucians	CT, MA	3	2
Aedes infirmatus	FL	1	1
Aedes sirrensis	CA	1	1
Aedes sollicitans	CT, NC, NJ	4	2
Aedes sticticus	AL, MA	3	3
Aedes stimulans	CT, MA	2	1
Aedes taeniorhynchus	FL, NC	3	3
Aedes triseriatus	IN	1	1
Aedes trivittatus	AL, IA, IN, OK, TN	6	6
Aedes vexans	AL, CA, CT, FL, IN, LA, MD, MI, MN, NH, NY, OK	16	10
Anopheles bradleyi	NC	2	1
Anopheles crucians	AL, FL	2	1
Anopheles freeborni	CA	1	1
Anopheles punctipennis	AL, IA, KY, MA, MD	7	3
Anopheles quadrimaculatus	LA, MA, MI, NY	5	4
Culex nigripalpus	FL	1	1
Culex pipiens	MI	1	1
Culex quinquefasctiatus	AL, FL, LA	3	2
Culex salinarius	MD, NC, NJ	3	2
Psorophora columbae	LA	1	1
Psorophora ferox	CT, FL	2	2

[a] Number of studies that report the collection of suspected *Dirofilaria immitis* in the mosquito species listed.
[b] Number of studies listed in the previous column in which third-stage larvae were present.
Data from Refs.[2,6,11]

Endosymbionts

Since 1975, bacterialike organisms were observed with the electron microscope in the cells of *D immitis* and other filarioids.[12] Research with molecular methods has shown that the organisms in *D immitis* are *Rickettsia*-like *Wolbachia* endosymbionts of arthropods.[13] In 1999, it was shown that tetracycline had negative effects on the embryogenesis of *D immitis*.[14] The effects of treatments targeting the *Wolbachia* organisms within *D immitis* will be discussed later in this article.

Life Cycle

The summary by Anderson in 2000 remains an excellent presentation of the generalities of the heartworm life cycle.[1] Following a single infection from mosquitoes, a dog

that develops adult worms can maintain a patent infection for up to 7.5 years.[10] The adult worms live in the pulmonary arteries of the canine host, and if the pulmonary artery is clamped just before euthanasia, worms are only found in the pulmonary arteries with none in the right ventricle.[15] However, when worms are present in a dog in massive numbers or in large numbers in small dogs, the worms may be regurgitated back into the heart, perhaps from a lack of space for the adult worms or blood pressure changes. In those instances in which adult worms back into the right ventricle and atrium to enter the vena cava, there can be massive hemolysis with associated clinical signs, leading to caval syndrome, a medical emergency.

Fertilized eggs undergo various developmental stages within the uterus: prelarva, developing embryo, pretzel, and stretched microfilaria.[16] Stretched microfilariae are free of the egg membrane, so that microfilariae exiting the vulval opening and entering the blood are not sheathed. Microfilariae transfused into dogs are capable of surviving for up to 2.5 years, and are capable of developing to the infective stage in mosquitoes for at least 3 months after transfusion.[10]

There are dynamics of the microfilarial interactions with dogs and mosquitoes that are very important for the parasite's transmission. There is no demonstrated correlation between circulating microfilarial numbers per cm^3 of blood and the number of adults present in pulmonary arteries.[10] Some homeostatic control is in place on the total number of microfilariae present within the peripheral blood, because microfilariae do not increase uncontrollably during chronic infection even though microfilariae probably live 2.5 years.[10] There is also a daily and seasonal variation in the number of microfilariae found in the blood of dogs.[10] On a daily basis, the circulating levels of *D immitis* microfilariae are defined as subperiodic, that is, the maximum number of microfilariae in circulation seems, in most geographic locations, to occur from late afternoon through late evening, but even at low levels, the peripheral blood contains 5% to 20% of the total microfilariae. Also, somewhat higher numbers of microfilariae are present in the blood of infected dogs in spring and summer compared with fall and winter. The daily and seasonal fluctuations in microfilariae numbers likely correlate with the presence of the vector, and it seems that the temporal availability of vectors within a geographic region can select for the local periodicity of the microfilariae.[17] Furthermore, the ingestion of too many microfilariae by a mosquito is fatal.[10] Mosquitoes can protect themselves somewhat against overwhelming infections by some minimal control of the number of microfilariae ingested in a blood meal from a microfilaremic dog, but they do not prevent ingestion of all microfilariae.[10]

In the mosquito, the microfilaria develops into a first-stage larva and after 2 molts becomes an infective third-stage larva. At 26±1°C in *Aedes aegypti* or *Aedes trivittatus*, the worms undergo a first molt in 7 to 8 days and the second molt a few days later (10 to 11 days after microfilarial ingestion).[18] Similar rates of development were noted for larvae in *Aedes albopictus* held at 28°C.[19] Thus, under constant temperatures of around 26°C (79°F) it takes 10 to 14 days for the larvae to reach the infective stage.[20] In North America where many geographic areas do not maintain steady temperatures near 26°C for much of the year, larval development within the mosquito is affected. These effects on larval development have been used to define expected periods of maps heartworm transmission in Canada and the United States.[21,22] These seasonality/transmission maps are based on Heartworm Development Units (HDUs). HDUs represent the number of Degree Days (°D) that the larval heartworm is above the threshold temperature for development, which has been determined to be 14°C (57°F). Thus, if the temperature is 15°C for 24 hours, this is 1°C above 14°C, so the larva gains 1 HDU; if the temperature is 26°C for 24 hours, this is 12°C above 14°C, so the larva accumulates 12 HDUs. A larva in a mosquito requires around 130

accumulated HDUs to become infective (10 days at 27°C; 20 days at 20.5°C).[21,23] To generate the HDU isolines on the maps for the beginning of the transmission season, a proposed "first date of transmission" is chosen, and then for each weather station's data, the temperatures reported for a day are converted to HDUs [daily °D value = (maximum daily temperature in °C – minimum daily temperature in °C/2] – 14°C; daily values less than 0°D are set to 0 because the larvae do not regress in their development). For the end of the transmission season, the last date of the year is chosen on which 130 HDUs could be accumulated in 30 days, the estimated life span of the mosquito at that time of year. In the map of the United States, it is theorized that transmission would only occur for all 12 months of the year in southern Florida and the extreme southern portion of Texas.[24]

Field studies have supported the HDU-based transmission models; one looked at sentinel dogs, one at collected mosquitoes, and one at yearling coyotes. A total of 96 heartworm-naïve adult beagles were placed in each of three sites in the southeastern United States (32 dogs per site): Tattnall County, Georgia, Orange and Lake Counties, Florida (different site in years 2 and 3), and Pointe-Coupee Parish, Louisiana.[25] The dogs were held in outdoor kennels or runs to allow mosquito access. Between April 1988 and April 1989, 20 dogs were placed at each site: 5 for a full year, and 5 for each of 3 4-month blocks (April to August, August to December, and December to April). Heartworms were found in 93% of the dogs held for a year, 86% of April to August dogs, 73% of August to December dogs, and 0% of December to April dogs. Due to the lack of infection in the latter group, additional dogs were placed at the sites from December through April in the next 2 years, and again, none of these dogs developed infections. HDU-based transmission start dates for these sites were the end of April for Louisiana and Georgia, and February or March for Florida; the stop dates were late October to early November in Louisiana and Georgia, and the first weeks of December in Florida. Molecular probes and polymerase chain reaction technology was used to examine the heads of nearly 110,000 mosquitoes (representing 17 different species) for the DNA of third-stage larvae of *D immitis*, in Florida and Louisiana.[26] The results supported the conclusion that heartworm transmission in the temperate Gulf coast region of the United States is seasonal rather than continuous. Seasonal heartworm transmission in coyotes in California was examined using coyote carcasses from three counties in north-coastal California (Mendocino, Sonoma, and Napa).[27] For 88 first-year coyotes killed from September through March (1994 to 2002), heartworms were not found in the pulmonary vasculature until the end of October. The HDU transmission season was calculated for the different years as starting from late May through early July and ending in varying weeks of October. Thus, these two studies seem to add good support for the suggested HDU transmission isolines.

There is no doubt that the majority of heartworm transmission occurs during the seasons predicted by the isoline numbers; however, there are reasons to suspect that transmission can be completed "off season." In 1983, Ernst and Slocombe pointed out that "temperatures below 14°C and above 37°C have been reported to be detrimental to mosquito survival. However, when these extremes of temperatures occur, individual mosquitoes may rest and survive where they are protected from temperature extremes."[28] It has also been shown that larvae in mosquitoes that cease development when cooled can resume and complete maturation when the mosquitoes are warmed,[21,28] that is, HDUs do not have to be consecutive. Heartworm larvae have been recovered from overwintering mosquitoes.[29] Furthermore, chilling mosquitoes to 12°C did not affect the viability of third-stage larvae after they were returned to normal conditions.[28] The canine sentinel study from 1988 to 1991 in the southeastern

United States occurred during a major drought, and lack of rainfall one year can have significant effects on mosquito disease transmission the next.[30] The research examining more than 100,000 mosquito heads was designed to examine seasonal prevalence, not to identify the potential transmission of heartworms by low numbers of mosquitoes in winter months, and the investigators state that "winter transmission of heartworms in Gainesville and Baton Rouge cannot be ruled out with absolute certainty."[26] Global climate change also needs to be built into the transmission model, as was suggested when the maps were first drawn.[31]

After the larvae leave the mosquito and enter the dog through the bite wound, they begin their development to the adult stage.[22,32–34] These third-stage larvae are not known to undergo any developmental arrest, that is, there is no apparent ability of the worm to halt the maturation process once it begins. Also, the timing of development is quite consistent, that is, larvae go through their two molts at a fairly defined time points after entry into the dog. The third-stage larvae that enter the dog are a millimeter or so in length.[18,22] Most of these larvae remain in the muscles at the site of inoculation, at least for the first 3 days (**Fig. 1**).[32] It would also seem that most larvae molt to the fourth stage probably before day 3 of the infection and before they begin to move any distance from the initial entry site.[22,32] Newly molted fourth-stage larvae are almost the same length as the infective third-stage larvae. Significant growth of the larvae begins at about 2 to 3 weeks after the infection is initiated, so that by 1 month post infection the worms are around 4 mm long, and by 2 months they are around 1 cm long (**Fig. 2**).

The molt to the adult stage occurs at about this time, between 50 and 58 days post infection.[22] The worms that first appear in the pulmonary arteries are 2 to 3 cm long. At this point, there is a rapid increase in size, and the worms can be 10 cm long by 4 months post infection, and 20 to 30 cm by the time they are 6.5 months old. Adult

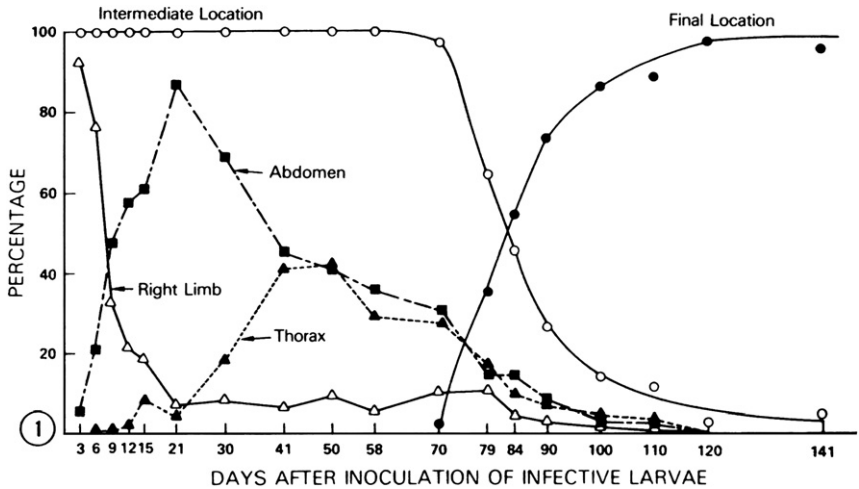

Fig. 1. Distribution and migration patterns of *D immitis* recovered from inoculated dogs, ○, total percentage of larvae recovered from the intermediate locations (subcutaneous and muscle tissues combined) throughout the body. Also included are worms from the abdominal and thoracic cavities, ρ, percentage recovered from the right hindlimb, ■, percentage recovered from the abdomen, π, percentage recovered in the thorax, ●, percentage recovered from final location (right side of the heart, pulmonary arteries, and vena cavae). (*From* Kotani T, Powers KG. Developmental stages of *Dirofilaria immitis* in the dog. Am J Vet Res 1982;43(12):2199–206; with permission.)

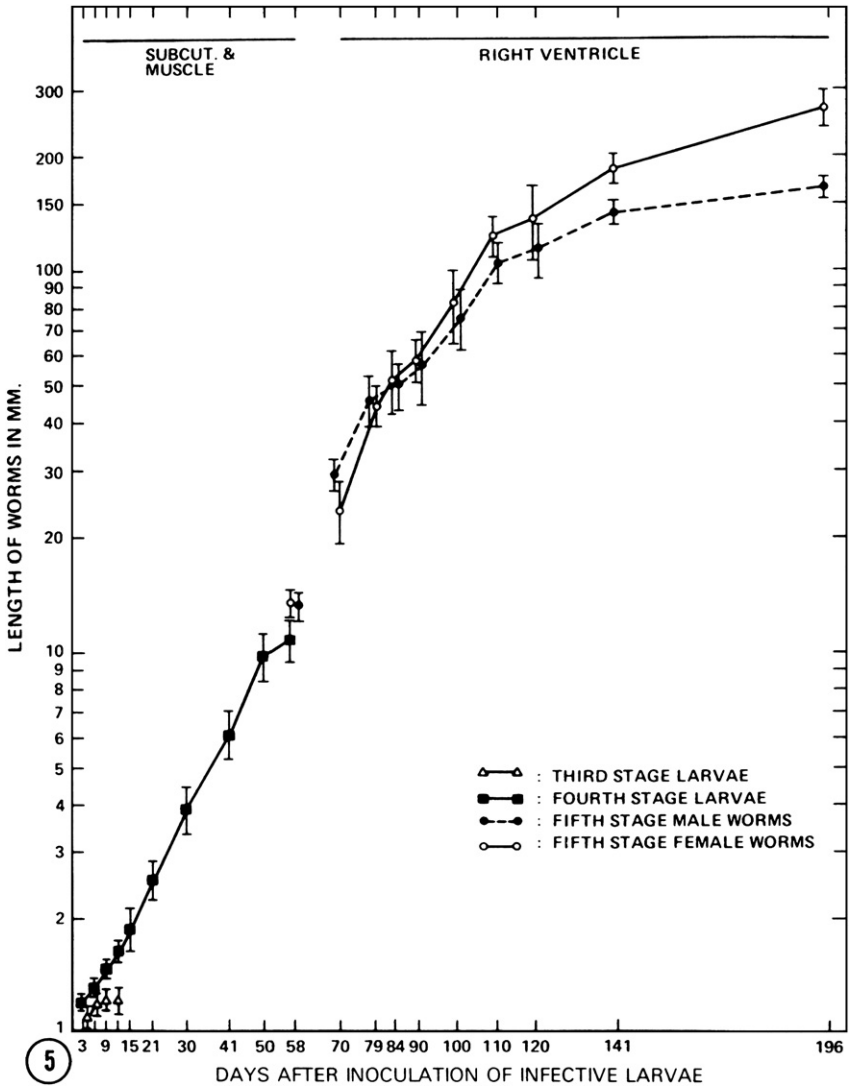

Fig. 2. Stages and larval growth during the maturation of *Dirofilaria immitis* in an experimentally infected dog. (*From* Kotani T, Powers KG. Developmental stages of *Dirofilaria immitis* in the dog. Am J Vet Res 1982;43(12):2199–206; with permission.)

males (12–20 cm long) are shorter and more slender than the females (25–31 cm long), and have a corkscrew-shaped tail that aids in copulation. Fertilization takes place in the pulmonary arteries when the females are approximately 4 months old and reach a length of 7 to 10 cm. Microfilariae first appear after 6 months to as late as 9 months after the induction of an experimental infection,[1] and patency may last up to 7.5 years according to one report.[10]

The route taken by the fourth-stage larvae to get from the abdominal and thoracic muscles to the pulmonary arteries has still not been fully elucidated. Worms entering

the pulmonary arteries are typically just a few centimeters long. However, even large adult worms are capable of extensive migration through the tissues.[35]

Life Cycle in the Domestic Cat

In cats, most of the inoculated worms do not mature, and the infections are typically not patent. Worms that survive apparently take longer to reach full maturity, because the prepatent period is 7 to 8 months in cats versus 6 months in dogs.[36] In natural infections, cats have one to eight worms, with two to four being most common.[36] It seems that worms in cats can live for up to 3 to 4 years, although approximately half of infected cats clear their infections without treatment within 3 years.[37]

Geographic Distribution

In recent years, there have been numerous surveys regularly reporting heartworm infections in animals in all of the United States with the exception of Alaska. Also, it is now accepted that most of the lower 48 states and Hawaii support the autochthonous transmission of *D immitis*, and that the disease can be considered enzootic within the canine population. Surveys have all revealed similar levels of prevalence: nationally, it is somewhat more than 1% in the pet population that visits veterinarians. The overall prevalence based on data from IDEXX reference laboratories and patient-side SNAP tests was around 1.4% (**Fig. 3**).[38] The highest level of infection was in the Southeast at 3.9%, with levels of 0.6% in the Northeast, 0.8% in the Midwest, and 1.2% in the West. This distribution is very similar to other surveys within the pet canine population.[39,40] In most of these studies, a fairly high prevalence was also observed along the Mississippi River (Arkansas 6.8%, Missouri 2.0%, Tennessee 3.6%).

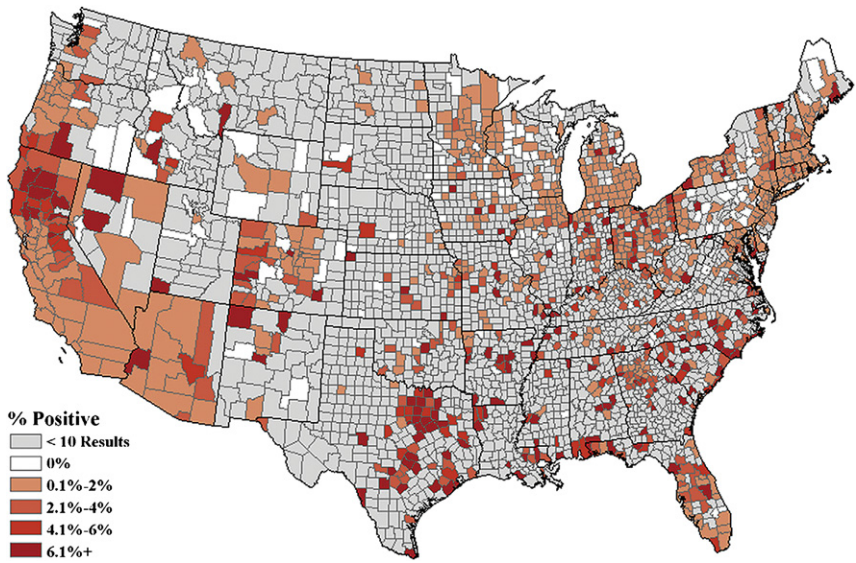

Fig. 3. Percentage of dogs testing positive for *D immitis* using the IDEXX Snap test by county throughout the United States. (*From* Bowman DD, Susan EL, Lorentzen L, et al. Prevalence and geographic distribution of *Dirofilaria immitis*, *Borrelia burgdorferi*, *Ehrlichia canis*, and *Anaplasma phagocytophilum* in dogs in the United States: Results of a national clinic-based serologic survey. Vet Parasitol 2009;160(1/2):138–48; with permission.)

Initially concentrated in the southeast and along the Mississippi River, heartworm over the last 50 years has become endemic in much of the United States due to movement of pets and hunting and show dogs.[41] The spread of heartworms has been fairly well documented. In Minnesota, heartworm was first recognized in 1937, but it rapidly spread after 1970.[41] In Canada, the spread has been monitored through a series of triannual surveys.[42] Heartworm is now present over a wide geographic area, is regularly documented in the western states, and endemic transmission is known to occur in California.[43]

The reason for the amazing spread of heartworms over the past few years is probably a combination of several factors. First, mosquito control in the United States was scaled back after the great success of mosquito abatement programs led to a reduction of mosquito-borne disease in humans and the public's fears about the overuse of pesticides. Second, as Dr Roncalli pointed out, pets have been moving rapidly in and out of heartworm-endemic areas, and this has probably exacerbated its spread.[41] Finally, the United States, unlike Europe, has an excellent reservoir host for heartworms: the American coyote, *Canis latrans*. The range of the coyote has expanded eastwardly in the last 50 years, and at the same time heartworms have spread in the coyote reservoir host, a trend that has been carefully detailed in California.[27] In the Sierra Nevada foothills, the prevalence of heartworm-positive coyotes in 1975 to 1985 was 35%, compared with 42% in 2000 to 2002; whereas in the Coastal Range foothills, prevalence increased from 10% to 44%, and in the San Francisco Bay foothills from 8% to 32%.

Cats also serve to give an indication of the distribution of canine heartworm. Cats are for the most part refractory to the development of patent heartworm infection, but adult worms can be found in the hearts of cats.[44] Throughout the United States, antibodies against *D immitis* have been detected in many cats, suggesting that they are being infected by larvae, even if the larvae do not grow into adults. Several national serologic studies of cats using a commercial feline heartworm antibody test found an antibody prevalence in 4.2% to 15.9%, with local prevalences reaching up to 33% in Auburn, California and 21% in Miami, Florida.[45–47]

The prevalence levels detected using antigen or microfilaria tests in dogs, necropsies in coyotes, and antibody tests in cats seem to correlate with the prevalence of the few human cases of *D immitis* reported in the United States. When the reported human cases are mapped on the 2001 American Heartworm Society survey map, it is obvious that human cases occur proportionally to the background prevalence in the dog population.[48]

Diagnosis of Infection

Any control program is based on the ability to diagnose an infection. For heartworm in dogs, the antigen detection assays are excellent diagnostic tests. These tests can be used to ascertain the heartworm status of a dog that has female worms that are greater than 6 months old. These tests should be used annually to verify that preventive programs in individual dogs are successful. The macrolide preventives, ivermectin, milbemycin oxime, moxidectin, and selamectin, result in a significant clearance of microfilariae from the blood of most dogs with circulating microfilariae in 6 to 8 months.[49–53] Therefore the only effective testing modality in the ever-increasing number of dogs receiving monthly preventative is an antigen detection assay.

Prevention

Since the introduction of Heartgard-30 (Merial) in 1987, prevention is achieved almost solely through the administration of one of the many macrocyclic lactones formulated

for monthly administration (or as a slow-release injectable formulation [ProHeart-6, Fort Dodge] that provides protection for 6 months; ProHeart-12, effective for 12 months, is available in other countries). The stage killed by the macrocyclic lactones during routine drug testing for monthly preventives is a larva that is 30 days old. In this process, dogs are infected with larvae from a mosquito, and then 30 days later (in a few cases, at 45 days) are given a single dose of the preventive. In most cases, the macrocyclic lactone is present in the body of the host for only a few days. This outcome is not true for moxidectin in the sustained-release formulation ProHeart-6 (Fort Dodge) and for the moxidectin in Advantage Multi [Bayer] that will reach a constant level in the body after several treatments.[50] After treatment, the worms are allowed to mature for 5 to 6 months, and necropsies are performed to assess the number of worms present in the pulmonary arteries of treated versus untreated control dogs. If any dogs develop a single heartworm during the initial trials, the product is likely not to receive approval by the Food and Drug Administration (FDA). In the case of the injectable product, Proheart-6, the dogs are given the injection, then 6 months later they are infected, and about 5 months afterward they are necropsied; here it is slightly more difficult to tell exactly what stage is being killed. It has also been shown that dogs infected with third-stage larvae and then treated 1 day later with the preventive dose of ivermectin are protected from developing adult heartworms.[51] Thus, it seems that ivermectin, and most likely the entire family of macrocyclic lactones, has efficacy against larvae between 1 and 30 days post infection in the dog. These drugs are highly efficacious against larvae up to 2 months of age, but after 2 months the efficacy of the macrocyclic lactones at preventive doses declines.[52]

Current prevention strategies are designed to start dogs on a monthly preventive product as early as possible in their life and continue administration for the life of the pet. There are advocates for year-round preventive therapy, and then others who recommend heartworm prevention only during the predicted seasons of transmission. A good treatment regimen should provide dogs with sufficient protection to allow them to remain heartworm-free even in areas with high infection pressure, where many mosquitoes are actively feeding on infected wildlife or unprotected pets. Adult heartworms are not affected by a single treatment of these macrocyclic lactone formulations, and these products are approved as safe for dogs with circulating microfilariae (selamectin [Revolution, Pfizer] and moxidectin [Advantage Multi, Bayer]) or without any significant effects, that is, only mild hypersensitivity reactions (milbemycin oxime [Sentinel Flavor Tabs, Novartis] and ivermectin [Heartgard Chewables for Dogs, Merial]).

In canine heartworm, the preventive products are not given at dosages designed to be completely microfilaricidal. Some 10% to 20% of dogs with patent infections that are placed on preventatives will continue to have circulating microfilariae for many months after beginning product administration (**Figs. 4** and **5**).[49,53] In a study examining the adulticidal activity of prophylactic doses of Heartgard Plus or Interceptor administered monthly for 16 months to dogs given heartworms by transplantation, some of the five dogs in each of the groups still had microfilariae in the blood after the eleventh (ivermectin) and sixth (milbemycin) treatments.[54] Similar results have been found in studies with selamectin and sustained-release moxidectin.[55,56] In a clinical field trial, seven dogs were given Heartgard and seven Heartgard Plus monthly for 2 years with blood being sampled for microfilariae every 3 to 5 months; two Heartgard dogs and one Heartgard Plus dog were positive 4 months after treatment.[57]

All current heartworm preventives belong to the same class of molecule, the macrocyclic lactones, and thus, one needs to be very prudent in our long-term stewardship of these drugs. Although resistance to macrolides in heartworms has been considered unlikely to develop, this was based on the assumption that preventives were being

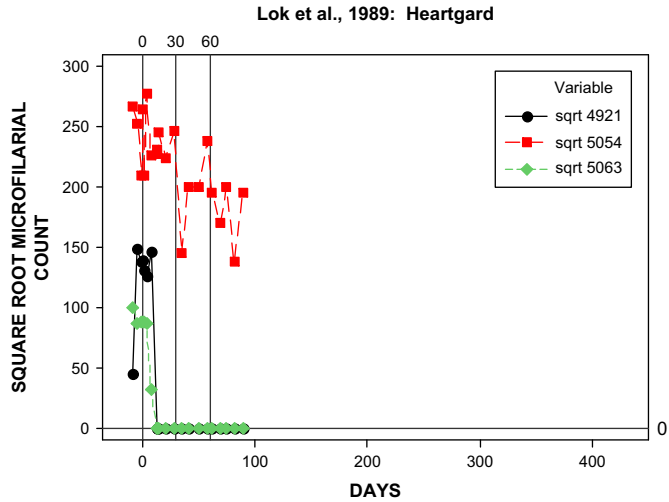

Fig. 4. Microfilarial counts (presented as square roots) in three dogs treated three times with ivermectin (Heartgard). The vertical lines represent the treatment event. Two of the dogs were negative soon after treatment, but one dog remained positive for circulating microfilariae with about 40,000 microfilariae per milliliter of blood. (*Data from* Lok JB, Knight DH, Ramadan EI. Effects of ivermectin on embryogenesis in *Dirofilaria immitis*: age structure and spatial distribution of intrauterine forms as a function of dosage and time posttreatment. In: Proceedings of the Heartworm Symposium. Charleston (SC); 1989. p. 85–94.)

used as per label instructions, and not as adulticides and microfilarial suppressants.[58] To minimize the opportunity for resistance to develop, the products should be used as approved by the FDA: as preventives that should be given to microfilarial negative dogs or to dogs that have been cleared of their heartworm infections.

The hope has been that the *Wolbachia* present in heartworms might prove to be an obligatory mutualistic relationship so that removal of the bacteria with antibiotics would lead to the death of its host, *D immitis*. However, the dog heartworm is not sufficiently dependent on its bacterial symbiont to be killed with simple prolonged antibiotic (doxycycline) therapy.[59] Nonetheless, the killing of *Wolbachia* may prevent the transmission of heartworms. Microfilariae from dogs treated with doxycycline were able to develop to the third larval stage in mosquitoes.[60] However, these larvae did not develop in dogs when they were inoculated subcutaneously. These studies are very difficult to perform, because of the need to grow infective-stage larvae from dogs with suppressed microfilarial counts. The four dogs used in the transmission trials received 40, 40, 6, and a non-disclosed number of infective-stage larvae. Although the controls given approximately 40 larvae were successfully infected while these worms from doxycycline treated dogs did not mature, the number of larvae tested remains small. The potential importance of this work suggests that it should be repeated with larger numbers of larvae and animals.

TREATMENT OF THE COMPANION ANIMAL

Treating the Canine Host

Pathophysiology

In the dog, the primary insult is damage to the pulmonary arteries and lung from the adult *D immitis* living in the pulmonary arteries. The severity of the lesions is related

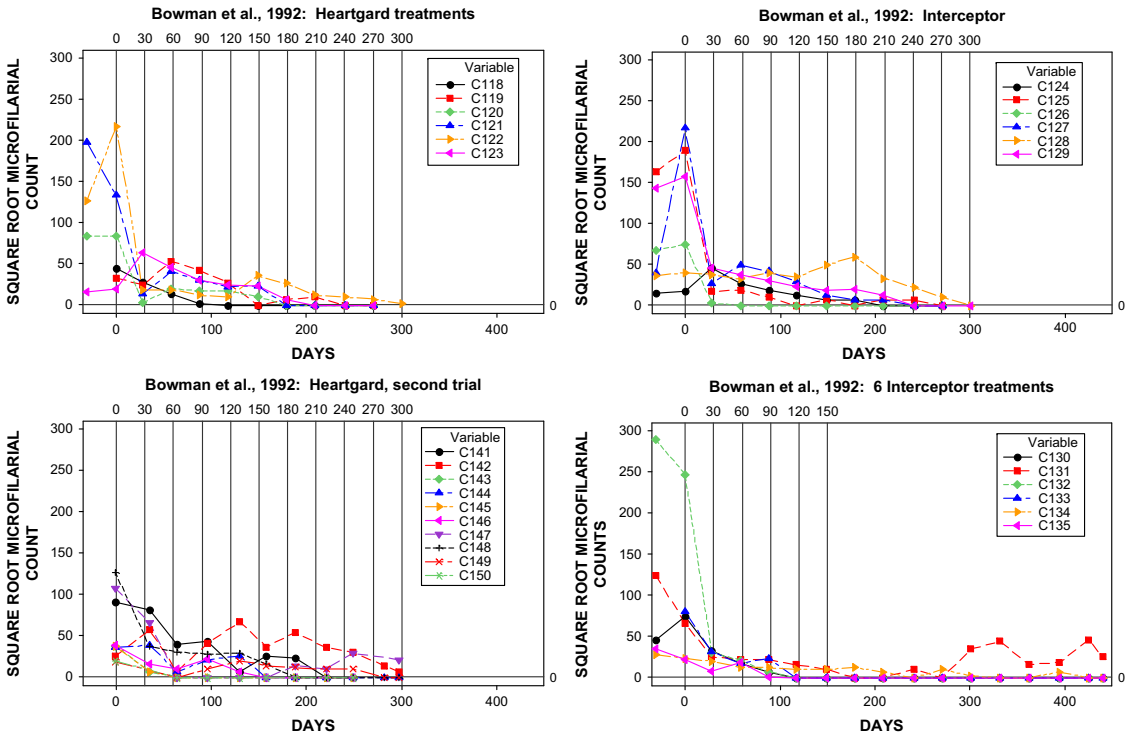

Fig. 5. Microfilarial counts in naturally infected dogs with patent infections treated with ivermectin (Heartgard) or milbemycin oxime (Interceptor) for extended periods. Counts were converted to square roots, and vertical lines on the graphs represent the days on which the dogs were treated. (*Top left*) Dogs treated with Heartgard experienced a precipitous drop in MF, but some dogs were still patent at 300 days post first treatment. (*Top right*) Dogs treated with Interceptor experienced a precipitous drop in MF, but four dogs were still positive at 270 days post first treatment. (*Bottom left*) Of the 10 dogs treated with Heartgard in the second trial, 2 dogs still had patent infections at 300 days. (*Bottom right*) After 6 monthly treatments of Interceptor, 2 dogs remained positive and 1 dog's MF counts appeared to be increasing in number after the termination of treatment. (*Data from* Bowman DD, Johnson RC, Ulrich ME, et al. Effects of long-term administration of ivermectin and milbemycin oxime on circulating microfilariae and parasite antigenemia in dogs with patent heartworm infections. In: Proceedings of the Heartworm Symposium '92. Austin (TX); 1992. p. 151–8.)

to the number of worms present (ranging from 1 to more than 250), amount of exercise, and the duration of infection. In most infections, the worms remain within the caudal pulmonary vascular tree, but they can on occasion migrate into the main pulmonary arteries, the right heart, and even into the great veins in heavy infections. When worms enter these atypical sites, the disease varies from the norm.

Many pathophysiological changes are associated with heartworm disease. The most marked and consistent anatomic pathologic change is a villous proliferation of the intima of the arteries containing worms. Other observed effects are vascular and pulmonary inflammation, pulmonary hypertension, disruption of vascular integrity, and fibrosis. Lesions in the pulmonary arteries appear soon after the arrival of the worms in the lungs. The first changes are endothelial damage and sloughing, villous proliferation, and the activation and attraction of leukocytes and platelets, which release factors that induce smooth muscle cell proliferation with collagen accumulation and fibrosis. The developing proliferative lesions may eventually encroach upon and occlude vascular lumina. Also, the induced endothelial swelling and altered intercellular junctions increase pulmonary vascular permeability. Fortunately, pulmonary infarction is uncommon because the gradual development of vascular occlusion allows extensive collateral circulation in the lung to compensate. For the same reason, obstruction of the pulmonary vessels by living worms is of little clinical significance unless there is a very high worm burden. On the other hand, worms that have died naturally or been killed by treatment induce thromboemboli, arterial obstruction, and vasoconstriction. These dead worms cause reactions by inciting thrombosis, granulomatous inflammation, and rugous villous inflammation. As the disease progresses, the pulmonary arteries become enlarged, thick-walled, and tortuous, with roughened endothelial surfaces.

In dogs with heartworm disease, the pulmonary arteries become varyingly thrombosed, thickened, dilated, tortuous, noncompliant, and functionally incompetent, with the vessels to the caudal lung lobes being the most affected. The damaged vessels cannot respond during increased oxygen demand and resulting diminished exercise capacity. The observed pulmonary vasoconstriction is partly secondary to excessive production of vasoactive substances by vascular endothelial cells.[61] Another contributing factor is hypoxia caused by ventilation-perfusion mismatching secondary to pulmonary thromboembolization, eosinophilic pneumonitis, or pulmonary consolidation. The end result of the prolonged vasoconstriction is pulmonary hypertension and compromised cardiac output.

The right heart's response to increased pulmonary pressure is initially an eccentric hypertrophy with chamber dilatation and wall thickening, Periods of increased cardiac output, such as during exercise, exacerbate the stress. In severe infections there may be decompensation (right heart failure). The response of the heart to modified hemodynamic stresses, geometric changes, and cardiac remodeling may contribute to secondary tricuspid insufficiency, thereby complicating or precipitating cardiac decompensation. Perivascular edema may develop due to the increased pulmonary vascular permeability. This fluid accumulation, along with an accompanying inflammatory infiltrate, may be evident radiographically as increased interstitial and even alveolar density. This presentation is seemingly of minimal clinical significance and should not be misinterpreted as an indication of left heart failure, that is, it is not cardiogenic pulmonary edema and furosemide is not indicated. The role of exercise in the development of pulmonary vascular disease and pulmonary hypertension is still not clear. Rawlings was unable to show an effect of 2.5 months of controlled treadmill exercise on pulmonary hypertension in heavily infected dogs,[62] whereas Dillon and colleagues[63] showed more severe pulmonary hypertension in lightly infected, mildly exercised dogs than in more heavily infected but unexercised dogs.

Generalized pulmonary parenchymal lesions sometimes can develop in heartworm infections. Eosinophilic pneumonitis is an inflammatory reaction to the immune-mediated clearance of antibody-coated microfilariae from the pulmonary microcirculation,[64] and it is therefore reported most commonly in naturally occurring occult heartworm disease (as opposed to iatrogenic occult infections induced by microfilaricidal treatment). Eosinophilic granulomatosis is an uncommon form of parenchymal lung disease associated with heartworm infection. This presentation is induced in a similar manner to eosinophilic pneumonitis, but in this case the trapped microfilariae are surrounded by neutrophils and eosinophils, eventually forming granulomas and associated bronchial lymphadenopathy.[65]

Focal pulmonary parenchymal lesions are more common than generalized disease, and are due to spontaneous or post-adulticidal pulmonary thromboemboli of dead or dying worms. Thromboembolization aggravates the development of pulmonary hypertension and right heart failure, and in rare instances may be the cause of a pulmonary infarction. Dead or moribund worms forced by the flow of blood down into the smaller vessels worsen vascular damage and enhance coagulation, which further restricts pulmonary blood flow and may even lead to consolidation of affected lung lobes. With acute and massive worm death, this insult may be profound, particularly if associated with exercise. The exacerbation of the disease that accompanies exercise likely reflects increased pulmonary arterial flow with escape of inflammatory mediators into the lung parenchyma through badly damaged and permeable arteries. It has been suggested that the lung injury induced by these disintegrating worms is similar to that seen in adult respiratory distress syndrome.

Glomerulonephritis caused by antigen-antibody complex deposition in the kidneys is common in heartworm-infected dogs. This condition results in a measurable proteinuria (albuminuria), and heartworm antigen can be detected in the urine of infected dogs. Progression to renal failure, however, is uncommon.

Heartworms may sometimes migrate to sites other than the pulmonary vasculature of the canine host. The signs associated with worms in atypical sites depend on the organ affected; worms have been described in muscles, brain, spinal cord, or anterior chamber of the eye. Worms have also been observed to migrate into the aortic bifurcation or more distally in the digital arteries.[66] Mature heartworms may sometimes move in a retrograde manner in the pulmonary arteries to the right heart and into the venae cavae, producing the life-threatening caval syndrome, described later.[67]

Clinical signs

Most dogs infected with heartworms show no signs. The clinical signs associated with chronic heartworm disease depend on the severity and duration of infection, and typically, reflect the effects of the parasite on the pulmonary arteries, lungs and, secondarily, the heart. The clinical history may elicit findings that weight loss, diminished exercise tolerance, lethargy, poor condition, cough, dyspnea, syncope, and abdominal distension. Physical examination of the affected animal may disclose evidence of weight loss, a split second heart sound (13%), right-sided heart murmur of tricuspid insufficiency (13%), and rarely cardiac gallop. In dogs with right heart failure, jugular venous distension and pulsation typically accompany hepatomegaly, splenomegaly, and ascites. It is atypical for a dog with chronic heartworm disease to have cardiac arrhythmias or conduction disturbances (<10%). Dogs with pulmonary parenchymal manifestations may have a cough and pulmonary crackles, and in the few dogs that develop eosinophilic granulomatosis there may be muffled lung sounds, dyspnea, and cyanosis. In a dog that has recently undergone massive heartworm-associated

pulmonary thromboembolization, fever and hemoptysis may be present; in such dogs the onset of signs is often associated with exercise.

Diagnosis

Microfilarial and antigen testing The presence of *D immitis* microfilariae in the blood or a positive antigen detection test can be used to confirm a clinical diagnosis of heartworm infection. Some enzyme-linked immunoassay (ELISA) antigen tests can quantitatively predict worm burdens, based on antigen concentrations. The semiquantitative ELISA (Snap Canine Heartworm PF) can predict antigen load and give some indication as to the number of worms present in an infection. The semiquantitative test is useful in predicting thromboembolic complications.[68]

Radiography Thoracic radiographs have been replaced by antigen tests as the routine verification method for heartworm infection. However, thoracic radiography offers an excellent method for determining disease severity and for assessing changes after treatment. In dogs with heartworms, radiographic abnormalities are present in approximately 85% of cases. Radiographic examination of 200 heartworm-infected dogs revealed that 70% had increased prominence of the main pulmonary artery segment, 60% had right ventricular enlargement, 50% had increased size and density of the pulmonary arteries, and 50% had pulmonary artery tortuosity and "pruning."[69] For dogs in right heart failure, additional changes might include enlargement of the caudal vena cava, liver, and spleen, pleural effusion, and ascites.

Different radiographic projections are superior for detailing different heartworm-associated changes. The ventrodorsal projection is preferable for cardiac silhouette evaluation and minimizing patient stress (**Fig. 6**A). The dorsoventral projection is superior for the evaluation of the caudal lobar pulmonary vessels, which are considered abnormal if larger than the diameter of the ninth rib where the rib and artery intersect. The lateral projection is best for the evaluation of the cranial pulmonary artery, which should normally not be larger than its accompanying vein or the proximal one-third of the fourth rib (**Fig. 6**B).

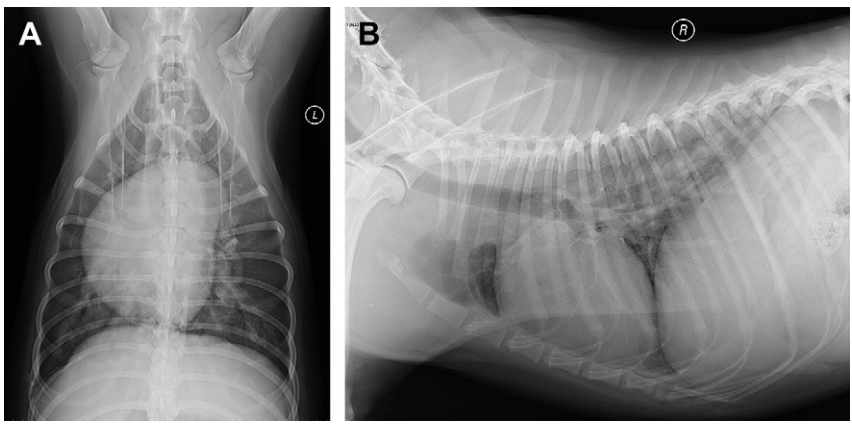

Fig. 6. Radiographs of a 3.5-year-old castrated male dog that had been adopted from a shelter in Georgia 10 months before presentation. (*A*) Ventrodorsal thoracic view showing the classic "reverse D" shape of the cardiac silhouette indicates right heart enlargement. The caudal lobar arteries are markedly enlarged and tortuous. (*B*) Lateral thoracic radiograph in which increased sternal contact is evident. The caudal lobar arteries are enlarged and tortuous in appearance. (*Courtesy of* Amie Knieper, Ithaca, NY.)

Damage to the pulmonary parenchyma is best evaluated radiographically. In pneumonitis, there is a mixed interstitial to alveolar density that typically is most severe in the caudal lung lobes. In eosinophilic granulomatosis, the inflammatory process appears as interstitial nodules associated with bronchial lymphadenopathy and, occasionally, pleural effusion. In pulmonary thromboembolism, there are coalescing interstitial and alveolar infiltrates, occurring particularly in the caudal lung lobes, reflecting the increased pulmonary vascular permeability and inflammation. With massive embolization or pulmonary infarction there may be the appearance of consolidation.

Echocardiography This method is insensitive as a diagnostic tool except in dogs with caval syndrome or heavy worm burdens, because heartworms are only rarely demonstrated in the right ventricle.[70] Two-dimensional echocardiography can sometimes demonstrate worms in the pulmonary artery. Echocardiography is a useful to assess right heart enlargement; with enlargement, the right ventricular end-diastolic dimension and septal and right ventricular free wall thickness will all be increased. It has been reported that 4 of 10 dogs with heartworm disease had abnormal (paradoxic) septal motion. In dogs with heartworm disease, the ratio of left to right ventricular internal dimension is often reduced from a normal value of 3 to 4 to a mean value of 0.7.

Electrocardiography Electrocardiography is useful in detecting arrhythmias, but a less useful method for detecting heartworm-induced chamber enlargement. Arrhythmias are rare in dogs with heartworm disease (2%–4%),[71] except in cases of caval syndrome and heart failure. A right ventricular enlargement pattern is supportive of heartworm disease.

Clinical pathology Hematological and serum chemical abnormalities are useful in providing a framework for evaluating concurrent disease in a dog that is going to undergo adulticide treatment. Dogs with heartworm disease may have a low-grade, nonregenerative anemia (10% of mildly to moderately affected dogs and up to 60% of severely affected dogs), neutrophilia (20%–80% of cases), eosinophilia (~85% of cases), and basophilia (~60% of cases).[45] Thrombocytopenia typically occurs 1 to 2 weeks after adulticidal therapy. In severe heartworm disease with heart failure, liver enzyme activities may be increased (10% of cases) and, occasionally, hyperbilirubinemia is noted. Azotemia is present in only about 5% of cases, and may be prerenal in origin if dehydration or heart failure is present, or may be secondary to glomerulonephritis. Albuminuria is present in 10% to 30% of cases, but if glomerular disease is severe, hypoalbuminemia may complicate the clinical picture.

Tracheobronchial cytology can be useful, particularly in the coughing dog with eosinophilic pneumonitis, occult heartworm disease, and cases with minimal supporting radiographic evidence; the examination is likely to reveal evidence of an eosinophilic infiltrate, and occasionally microfilariae. In cases of congestive heart failure, abdominal fluid analysis reveals a modified transudate. Dogs with right heart failure secondary to heartworm disease have a central venous pressure that range from 12 to more than 20 cm H_2O, but ascites can develop at lower pressures if hypoalbuminemia is present.

Microfilaricidal and Preventive Therapy in Heartworm-Positive Dogs

When considering adulticide treatment, a minimum clinical database usually consists of an antigen test, a microfilarial test, chemistry panel, complete blood count (CBC), urinalysis, thoracic radiographic evaluation and, if liver disease is suspected, a serum bile acid evaluation. At this time, monthly macrolide preventive is prescribed. This approach, currently recommended by the American Heartworm Society,[72] is to

prevent further infection, reduce circulating microfilariae, and kill larval stages not yet susceptible to adulticide therapy. Dogs with circulating microfilariae should be kept under observation after the first macrolide dose so an adverse reaction might be recognized and promptly treated. Corticosteroids with or without antihistamines (dexamethasone at 0.25 mg/kg intravenously and diphenhydramine at 2 mg/kg intramuscularly, or 1 mg/kg of prednisolone orally 1 hour before and 6 hours after administration of the first dose of preventive) may be given to reduce the potential for adverse reaction in the highly microfilaremic patient. Adverse reactions are unusual with macrolides at preventive doses, but caution should be exercised. Some allow up to 2 to 3 months to lapse after the end of the heartworm transmission season to allow any larvae to mature to adults before commencing adulticide therapy, whereas if the diagnosis is made in the spring or late winter, when infective larvae have matured, adulticidal therapy may be immediately administered.

Adulticidal therapy

Melarsomine dihydrochloride In heartworm disease, the goal of therapy is usually to kill the worms to prevent additional damage to the pulmonary vasculature. The only drug approved currently for this purpose is the organoarsenic compound melarsomine dihydrochloride (Immiticide). With two doses (2.5 mg/kg intramuscularly every 24 hours for two treatments), the efficacy is greater than 96%. The efficacy increases to 99% efficacy with a repeat of the two-dose therapy in 4 months or with a split dosing regimen whereby a single dose is followed by a 2-dose regimen in 1 to 3 months. This product is much safer than the previously prescribed thiacetarsamide, but adverse reactions do occur.

Melarsomine kills the large adults that are carried deeper into the lungs by the vascular flow in the pulmonary arteries. Thromboembolic events are expected following successful adulticide therapy, and the severity of the sequelae can be decreased through strict exercise restriction after melarsomine administration. Cage rest is most easily assured and verified in the veterinary clinic. If financial constraints preclude hospitalization, the owner should be advised that this is an important part of the therapy, and it may be necessary to provide tranquilizers to keep the pet calm at home. The owner needs to be made to understand that failure to restrict the exercise of the pet can increase the opportunity for thromboembolic events that can prove fatal. Patients treated with the split-dosing regimen have a higher seroconversion rate to a negative antigen status than patients treated with the standard dosing regimen.[73] Also, the split-dose method kills only a portion of the worms following the initial intramuscular injection, which lessens the chance of thromboembolic complications. The first dose is then followed in 1 to 3 months with the two-dose regimen. The disadvantages of this method are the additional expense, an increased total arsenic dose, and the need for 2 months of exercise restriction. In 55 dogs with severe heartworm disease treated with the split-dosing method, 96% had a good to very good outcome, with more than 98% testing negative for circulating antigen 90 days post therapy.[74] Of these 55 dogs, 31% had "mild or moderate pulmonary thromboembolization," and there were no fatalities. After treatment, the most common signs were fever, cough, and anorexia that occurred 5 to 7 days later. Signs were associated with mild perivascular caudal lobar pulmonary radiographic densities that subsided spontaneously or after corticosteroid therapy.

Surgical removal of the worms Worms can be removed using flexible alligator forceps.[75] A description of this method in 36 dogs with mild and severe heartworm disease was found to be 90% effective; 2 of the 9 severely affected dogs died of heart and renal

failure within 3 months of surgery. In skilled hands, the technique is apparently safe, and subsequent studies have demonstrated superior results as compared with melarsomine, producing less pulmonary thromboembolization and caval syndrome.[76] Dogs treated surgically still require melarsomine treatment to provide a complete cure. The advantages of surgical removal are the diminished potential of arsenic toxicity and fewer worms to cause thromboembolic disease. Of course, disadvantages include the need for general anesthesia and fluoroscopy, as well as the incomplete abrogation of all arsenical use.

Macrolides The macrolides are now known to have some adulticidal properties when administered at the dosages used for preventive therapy.[54] Ivermectin administered monthly at the preventive dose for 31 consecutive months was nearly 100% efficacious in clearing dogs of their heartworm infections.[52] Selamectin, when administered for 18 months at the preventive dose, killed approximately 40% of transplanted worms.[55] Milbemycin and sustained-release moxidectin also seem to have minimal adulticidal efficacy when administered at the preventive dose.[54,55] For different reasons, including the length of treatment required, the lack of control over the thromboembolic events that will occur in the patient, and the potential for induction of resistance as discussed earlier, the current recommendation is that macrolides not be adopted for adulticide therapy.

Post-Adulticide Antigen Testing

Antigen detection is now used to assess the efficacy of adulticide therapy. Circulating antigen will typically become undetectable 8 to 12 weeks after successful therapy; thus, a positive test 12 weeks after completed adulticide therapy suggests a persistent infection.[49] There are cases, however, when the antigen tests may remain positive for longer periods, and one should probably not assume a failure of adulticidal therapy unless antigen is detected $\geq$6 months after therapy has concluded.

Supplemental Therapy

There are several classes of supplemental or ancillary therapy used concurrently with melarsomine therapy; the most common are corticosteroids, aspirin, heparin, and doxycycline. These therapies all have proponents and detractors, and the perceived value of each waxes and wanes every few years. However, it is likely that they all can have value in the hands of certain practitioners in certain cases.

Corticosteroids The agent most often advocated for use in heartworm disease is prednisone, which reduces pulmonary arteritis but worsens the proliferative vascular lesions, diminishes pulmonary arterial flow, and reduces adulticide efficacy. Thus, corticosteroids are indicated only when there are adverse reactions to microfilaricides, pulmonary parenchymal complications, and perhaps to minimize tissue reaction to melarsomine. For allergic pneumonitis, prednisone (1 mg/kg/day) administered for 3 to 5 days and discontinued or tapered as indicated, generally has a favorable outcome.[45] Prednisone at 1 to 2 mg/kg per day with cage rest has been advocated for use in the management of pulmonary thromboembolization, with the treatments being continued until radiographic and clinical improvement are noted.[45] The associated steroid-induced fluid retention is the reason that such therapy should be used with caution when the patient is in borderline heart failure.

Aspirin Antithrombotic agents have been examined numerous times relative to heartworm disease. However, the more recent work has indicated that there are no significant differences in severity of pulmonary vascular lesions between aspirin-treated

and control dogs. Thus, the American Heartworm Society no longer endorses aspirin therapy for routine treatment of heartworm disease.[72]

Heparin Heparin therapy has not been studied with respect to melarsomine adulticidal therapy. Low-dose calcium heparin was shown to reduce the adverse reactions associated with thiacetarsemide in dogs with severe clinical signs, including heart failure.[77]

Doxycycline With the realization that *Wolbachia* may contribute to the pathogenesis associated with heartworm infection, efforts to clear *Wolbachia* have been examined in several studies.[60,78] Using surgically transplanted worms, it was shown that a combination of weekly ivermectin (weekly at the monthly preventive dose) and daily doxycycline (10 mg/kg/day) eliminated microfilariae, reduced pulmonary thromboembolization after melarsomine therapy, and reduced heartworm burden compared with control dogs by 78% after 9 months of therapy.[59]

Post-adulticide microfilaricidal therapy

Microfilaricidal therapy has traditionally been instituted 3 to 6 weeks after adulticide administration.[45] Microfilariae are rapidly cleared with ivermectin at 50 μg/kg or milbemycin at 500 μg/kg. Using ivermectin at the 50 μg/kg dose caused adverse reactions (shock, depression, hypothermia, and vomiting) in 8 of 126 dogs receiving ivermectin 3 weeks after adulticide therapy. All dogs recovered within 12 hours after treatment with fluids and corticosteroids; however, one of the 8 dogs died 4 days later. Dogs treated with milbemycin at 500 μg/kg or the elevated ivermectin dose (50 μg/kg) should be hospitalized and observed on the day of treatment. Small dogs (<16 kg) with high microfilarial counts (>10,000/mL) are more apt to suffer adverse reactions.[79] Diphenhydramine (2 mg/kg intramuscularly) and dexamethasone (0.25 mg/kg intravenously) are often administered prophylactically to prevent adverse reactions to microfilaricidal doses of macrolides. Dogs typically are now treated by simply beginning them on a monthly preventive at the time of, or 3 to 6 weeks after the completion of the adulticide therapy.

Complications and specific syndromes

Treating the dog that has no signs from its heartworm infection The typical dog treated for heartworms is an antigen or microfilarial-positive dog with no clinical signs. The dog may have no signs even though it has demonstrable radiographic lesions. Recommended treatment is the split-dose (3) melarsomine regimen. Dogs without signs may develop clinical signs after adulticide therapy due to the induced pulmonary thromboembolization and lung injury following worm kill. The risk of post-adulticide signs can be predicted to some extent using an antigen test to derive a semiquantitative estimate of worm burden and radiographs to assess the existing lung damage.[68] A dog with severe radiographic lesions is not likely to tolerate the treatment as well as one that does not, but radiographic signs do not necessarily correlate directly to worm burden.

Glomerulonephritis Chronic heartworm infection may be associated with glomerulonephritis, which can be severe. The glomerular lesions caused by heartworms are unlikely to produce renal failure, but heartworm infection in a dog with proteinuria and azotemia presents the clinician with a therapeutic dilemma. The worms need to be removed because they contribute to the disease, but doing so carries risks. One approach is to hospitalize the patient and administer intravenous fluids (lactated Ringer solution at 2 to 3 mL/kg/h) for 48 hours (beginning 12 hours before the first melarsomine dose). It is then recommended that the patient return after 48 hours for a blood urea nitrogen and creatinine determination. The second portion of the

split-dose treatment is then scheduled for 1 to 3 months later depending on renal function and the response of the patient to the first adulticide administration.

Eosinophilic pneumonitis Eosinophilic pneumonitis affects some 14% of dogs with heartworm disease within the early stages of infection.[45,64] Signs may include cough, dyspnea, weight loss, and exercise intolerance. Radiographs show typical changes associated with heartworm disease with an interstitial infiltrate that is usually worse in the caudal lung lobes. The administration of corticosteroids often results in the rapid attenuation of clinical signs, with radiographic clearing in less than a week. If the signs are ameliorated by the treatment, adulticidal therapy can be started.

Eosinophilic granulomatosis Eosinophilic granulomatosis is a rare presentation in heartworm disease that does not respond as well to treatment as eosinophilic pneumonitis, is characterized by a more organized, nodular inflammatory process associated with bronchial lymphadenopathy, and sometimes accompanying pleural effusion. Cough, wheezes, and pulmonary crackles are often audible; treatment consists of increased levels of prednisone relative to those for eosinophilic pneumonitis, it may take up to 2 weeks for signs to clear, and ultimately, the surgical excision of lobar lesions may be required to control the disease.

Congestive heart failure Right heart failure is caused by increased right ventricular afterload (secondary to chronic pulmonary arterial disease and thromboemboli with resultant pulmonary hypertension). Severe and chronic pulmonary hypertension is often complicated by right heart failure and secondary tricuspid regurgitation. Up to 50% of dogs with severe heartworm-associated pulmonary vascular complications will develop heart failure.[45] Clinical signs may include weight loss, exercise intolerance, ashen mucous membranes with prolonged capillary refill time, ascites, dyspnea, jugular venous distension and pulsation, arrhythmias with pulse deficits, and adventitial lung sounds (crackles and possibly wheezes).

Treatment aims at the reduction of signs of congestion, reducing pulmonary hypertension, and increasing cardiac output. This therapy involves dietary, pharmacologic, and procedural interventions. If congestive heart failure is present before adulticidal therapy, the question arises as to whether melarsomine should be administered. If clinical response to heart failure management is good, adulticidal therapy may be offered in 4 to 12 weeks, as conditions allow, but the adulticide is generally avoided if the heart failure remains refractory to treatment.

Caval syndrome Caval syndrome is an uncommon but severe complication of heartworm disease, characterized by a heavy worm burden (usually >60 worms) and a poor prognosis. Most cases occur in male dogs (75% to 90%). Caval syndrome is due to the retrograde migration of adult heartworms from the pulmonary arteries into the venae cavae and right atrium, which produces partial inflow obstruction to the right heart and, by interfering with the valve apparatus, producing tricuspid insufficiency (with resultant systolic murmur, jugular pulse, and increase in central venous pressure). These dogs have preexisting heartworm-induced pulmonary hypertension, as well as existing or developing cardiac arrhythmias that further compromise cardiac function.

Clinical signs include a sudden onset of anorexia, depression, and weakness, which may occasionally also present with coughing, dyspnea, hemolytic anemia, hemoglobinemia, hemoglobinuria, and hepatic or renal dysfunction. Hemoglobinuria is considered pathognomonic. Hemoglobinemia and microfilaremia have been reported in 85% of dogs suffering from caval syndrome. Physical examination reveals pale mucous

membranes, prolonged capillary refill time, weak pulses, jugular distension and pulsation, hepatosplenomegaly, and dyspnea. Thoracic auscultation may disclose a systolic heart murmur of tricuspid insufficiency (87% of cases); loud, split S2 (67%); and cardiac gallop (20%). Other reported signs are ascites (29%), jaundice (19%), and hemoptysis (6%). The body temperature may be subnormal to mildly elevated. Thoracic radiography will reveal signs typical of severe heartworm disease. Sonography reveals heartworm echo shadows.

The hemolytic anemia is caused by the lysis of to red blood cells (RBCs) passing through the sieve of heartworms now in the right atrium and venae cavae. The intravascular hemolysis, along with the induced metabolic acidosis and diminished hepatic function, contributes to an impaired removal of circulating procoagulants. This situation leads to disseminated intravascular coagulation (DIC) with the RBCs being lysed as they are forced past fibrin strands in capillaries, causing further DIC development. The reason for the hepatorenal dysfunction is not clear, but it is likely due to the effects of passive congestion, diminished perfusion, and effects of hemolysis byproducts. Without treatment, death often occurs within 24 to 72 hours.

Hematology and clinical chemistries reveal numerous abnormalities. Hematology will typically show moderate regenerative anemia. The normochromic, macrocytic anemia is associated with the presence of target cells, schistocytes, spur cells, and spherocytes. Leukocytosis with neutrophilia, eosinophilia, and left shift has been described. Dogs with DIC will have thrombocytopenia and hypofibrinogenemia, as well as a prolonged one-stage prothrombin time (PT), partial thromboplastin time (PTT), activated coagulation time (ACT), and high fibrin degradation product concentrations. Serum chemistry analysis typically reveals increases in liver enzymes, bilirubin, and indices of renal function.

Urine analysis reveals high bilirubin and protein concentrations in 50% of cases and more frequently, hemoglobinuria. Central venous pressure is high in some 80% to 90% of cases (mean, 11.4 cm H_2O). Electrocardiographic abnormalities include sinus tachycardia (33% of cases) and atrial and ventricular premature complexes (28% and 6%, respectively). Worms within the right atrium with movement into the right ventricle during diastole are evident echocardiographically; this finding is nearly pathognomonic for caval syndrome when observed with the associated signs. The right ventricular lumen will be enlarged and the left diminished in size; this is probably caused by pulmonary hypertension accompanied by reduced left ventricular preload. Paradoxic septal motion, caused by high right ventricular pressure, is commonly observed.

If the offending heartworms are not removed from the right atrium and venae cavae the prognosis is poor, and even with removal, mortality may occur in almost half of the cases. Fluid therapy is required to improve cardiac output and tissue perfusion, for treating DIC, to prevent hemoglobin nephropathy, and to aid in the correction of metabolic acidosis; however, excessive fluid therapy may precipitate or worsen signs of congestive heart failure. Broad-spectrum antibiotics and aspirin should be administered.

The surgical removal technique for heartworm in dogs with caval syndrome was developed by Jackson and colleagues.[80] This procedure should be undertaken as early as is practical. Sedation is often unnecessary, and the procedure can be accomplished with only local anesthesia. The dog is restrained in left lateral recumbency, the jugular vein is isolated distally and ligated proximally (craniad), and alligator forceps (20 to 40 cm long, preferably of small diameter) are guided gently down the vein past the thoracic inlet Fluoroscopic guidance, when available, can be helpful. A good working goal is the removal of 35 to 50 worms or several consecutive unsuccessful passes, once the worm burden has been reduced. After worm removal has

been completed, the jugular vein is ligated distally and the skin incision closed with sutures. Successful worm retrieval is associated with an almost immediate reduction in the intensity of the cardiac murmur and jugular pulsations, rapid clearing of hemoglobinemia and hemoglobinuria, and normalization of serum enzymatic aberrations. Cardiac function should improve immediately with latent improvement during the next 24 hours. The removal of worms does not reduce right ventricular afterload (pulmonary hypertension), and therefore, fluid therapy must be monitored carefully before and after surgery to avoid precipitation or worsening of right heart failure. Cage rest must be enforced for as long as it is deemed necessary. The anemia is likely not to resolve until 2 to 4 weeks after worm removal.

Once the animal has recovered from its crisis, arrangements can be made for the split-dose adulticide therapy to remove whatever worms remain after a month or more. Macrolide preventive therapy is administered just before release from the hospital. Before initiating adulticide therapy, it is important to assess liver and renal function. Often in these cases, aspirin therapy is continued for 3 to 4 weeks after adulticide therapy.

Aberrant migration Young adult worms occasionally appear in locations other than the pulmonary arteries. Worms have been found in the brain, spinal cord, epidural space, anterior chamber of the eye, the vitreous, the subcutis, the peritoneal cavity, and the iliac and femoral arteries. Treatment of heartworms in ectopic locations ranges from no treatment (eg, peritoneal cavity), to surgical excision, adulticidal therapy, or symptomatic treatment (eg, seizure control in the case of brain migration). A method for surgical removal of the worms from the internal iliac and femoral arteries has been described.[66]

Prognosis

When not accompanied by clinical signs, the prognosis for heartworm infection is generally good. The prognosis for severe heartworm disease must be guarded, but most cases can be successfully managed. After the initial crisis and adulticidal therapy, resolution of underlying manifestations of chronic heartworm disease begins, and amazingly many of the changes including the intimal proliferation are partially reversible.[81] The prognosis is poorest when initial presentation is associated with severe DIC, caval syndrome, massive embolization, eosinophilic granulomatosis, severe pulmonary arterial disease, and heart failure. Radiographic and arteriographic lesions usually begin to resolve within 3 to 4 weeks of adulticide therapy, and pulmonary hypertension is reduced within months. Pulmonary parenchymal changes are worsened during the 6 months after adulticidal therapy, but begin to improve and often resolve in the next 2 to 3 months. Persistence of parenchymal lesions suggests that the adulticide therapy may not have been fully successful. Also, signs of heart failure should disappear with the aid of symptomatic therapy, cage rest, and successful removal of all worms.

Treating the Feline Host

The cat can develop disease associated with *D immitis* infection, but infections with mature worms only occur at 5% to 20% of the prevalence that would occur in an unprotected dog population in the same environment.[82] It is more difficult to infect a cat than a dog, and less than 25% of administered third-stage larvae develop to adulthood in cats. Naturally infected cats typically have less than 10 worms and usually only 1 to 4 worms. Cats tend not to support patent infections, thus there is a high percentage of infected cats that have no microfilaremia or very low microfilarial

counts. Adult worms also do not live as long in the cat, although a few survive for up to 4 years.[37,83] Heartworm infection has been found in up to 14% of shelter cats.[82] In well-cared-for cats in Texas and North Carolina, heartworm disease with adult worms was diagnosed in 9 of 100 cats with cardiorespiratory signs.[84] Of the 100 Texas and North Carolina cats, 26% had antibodies to *D immitis*, suggesting that they had been host to third-stage larvae that did not fully mature.[84] Aberrant worm migration seems to be a greater problem, or a problem with more severe sequelae, in cats than in dogs.

Pathophysiology

It seems that in cats, more so than in dogs, the immature adult heartworms that enter the lungs cause disease even if they do not mature to adult worms or result in patent infections. This finding has been demonstrated radiographically in experimentally infected cats,[85] and pulmonary vascular lesions have been observed in naturally infected cats with no adult worms.[86] Moreover, pharmacologically abbreviated infections in cats (the worms being killed before becoming adults) has revealed that these infections produce not only proliferative and inflammatory lesions in the pulmonary arteries, but in the bronchioles and lung parenchyma as well. This disease, in which there are respiratory signs due to heartworms but no adult worms, has been termed "heartworm-associated respiratory disease" (HARD) or "pulmonary larval dirofilariasis."[36] Thus, in the cat, pulmonary larval dirofilariasis will produce asthma-like clinical signs even though the worms never fully mature. It is now recognized that 38% to 74% of cats with mature *D immitis* develop clinical signs, as do an estimated 50% of those that never develop mature infections.[36,83]

The worms entering the lungs of cats are around 2 to 3 cm long. The size of the worms relative to the lungs of the cat (versus the dog) along with the presence in cats of pulmonary intravascular macrophages may be reasons why pulmonary inflammation is worse in cats than in dogs.[87] When adult worms were transplanted into heartworm-naïve cats, the significant pulmonary enlargement 1 week after the transplant suggested an intense host-parasite interaction.[88] Cats also exhibit a severe myointimal and eosinophilic response to helminth infections, including to *D immitis*, which produces pulmonary vascular narrowing and tortuosity, thrombosis, and possibly pulmonary hypertension.[89] The feline pulmonary arterial tree is smaller than that of the dog and has less collateral circulation; therefore embolization, even with small numbers of smaller worms, produces disastrous results that can be associated with infarction and even death. Although rare, cor pulmonale and right heart failure can be associated with chronic feline heartworm disease, and the latter is manifested by pleural effusion (hydrothorax or chylothorax), ascites, or both. The lung of the heartworm-infected cat will develop eosinophilic infiltrates in the parenchyma (pneumonitis) and pulmonary arteries. Also, pulmonary vessels may leak plasma, producing pulmonary edema (possibly acute respiratory distress syndrome) and type II cell proliferation, both potentially altering O_2 diffusion.[88] Radiographic findings in cats suggest air trapping, compatible with bronchoconstriction. Overall, cats that have been infected with heartworms can develop multifaceted disease that can vary from virtually no signs to diminished pulmonary function, hypoxemia, dyspnea, cough, and even death.

Clinical signs

Clinical manifestations of heartworm disease in cats can be peracute, acute, or chronic.[84,88,90] Signs in acute or peracute presentations that probably represent cases of worm death, embolization, or aberrant migration variably include: salivation, tachycardia, shock, dyspnea, hemoptysis, vomiting and diarrhea, syncope, dementia,

ataxia, circling, head tilt, blindness, seizures, and death. In these acute cases, postmortem examination often will reveal pulmonary infarction with congestion and edema. Except in the acute or peracute cases, the physical examination of cats with heartworm infection or disease is often unrewarding, although a murmur, gallop, or diminished or adventitial lung sounds (or a combination of these findings) may be noted. In addition, cats may be thin, dyspneic, or both. If heart failure is present, jugular venous distension, dyspnea and, rarely, ascites are detected. In a retrospective study, 28% of cats with mature heartworms seen at a referral center were presented by the owners for signs not referable to the *D immitis* infection.[90] The reported historical findings in cats with chronic heartworm disease include: anorexia, weight loss, lethargy, exercise intolerance, cough, dyspnea, vomiting, and on rare occasions signs of right heart failure. Dyspnea and cough are consistent findings and, when present, should raise suspicion of heartworm disease, especially in endemic areas.[90] Chylothorax, pneumothorax, and caval syndrome have been recognized as rare manifestations of feline heartworm disease.

Diagnosis

Heartworm infection in cats poses a diagnostic problem. Clinical signs are often absent, and if present, are different from those of the dog. The overall prevalence of heartworm in cats is low, so suspicion is lessened. The immunologic tests are often falsely negative in the cat, and microfilariae are usually not present. Electrocardiographic findings are minimal, and radiographic signs are inconsistent and transient.

Microfilarial and antigen testing Because most cats infected with heartworms do not have patent infections, microfilarial testing is not useful. Antigen-positive cats nearly always have more than one mature *D immitis* female, and antibody-positive/antigen-negative cats are not usually be infected with an adult female *D immitis*. However approximately 50% of antibody-positive/antigen-negative cats develop HARD/pulmonary larval dirofilariasis.

Antigen tests are imperfect in cats because of low worm burdens and the fact that only female worms produce detectable antigen.[91] Even in cats that develop detectable numbers of worms, disease can develop before the worms are mature enough to produce antigen.[92]

Screening for antibodies allows a suspicion of pulmonary larval dirofilariasis to be given additional weight, and allows clinicians to alert pet owners of the potential need for further diagnostics. Out of 1962 cats positive for antibodies to heartworms, only 18.6% were antigen positive. About half the cats that are antibody-positive and antigen-negative have postmortem manifestations of heartworm disease. Also, the antibody-positive status of infected cats that clear infection does wane with time.

Radiography Cats without clinical signs rarely have lesions that appear on thoracic radiographs.[83] The most sensitive radiographic criterion (left caudal pulmonary artery greater than 1.6 times the ninth rib at the ninth intercostal space on the ventrodorsal projection) is detected in only about half the cases.[85] Also, the lesions in cats are not specific and are often transient; cats develop lesions when the worms first reach the lungs and these changes can be seen on necropsy even if the worms fail to fully mature.[93] Radiographic findings, when present, include enlarged caudal pulmonary arteries, often with ill-defined margins, pulmonary parenchymal changes that include focal or diffuse infiltrates (interstitial, bronchointerstitial, or even alveolar), perivascular density and, occasionally, atelectasis.

Echocardiography Echocardiography is much more sensitive in cats than in dogs.[84] A double-lined echodensity typically is evident in the main pulmonary artery, one of its branches, the right ventricle, or occasionally at the right atrioventricular junction. Heartworms are found by echocardiography in about three-fourths of cats that have worms in their pulmonary arteries or right ventricle.[84]

Prevention and treatment

There is no reason to screen cats for heartworm infection before beginning them on prophylaxis because there are no microfilariae to speak of, so no risk of a reaction to dying microfilariae. Also, the heartworm preventives have been examined as part of the safety package submitted to the FDA to show that they are not adulticidal. Thus cats, unlike dogs, can be started on a preventive program without prior testing.

Whether preventives should be recommended for cats is a common question by owners and practitioners alike. In the southeastern United States, somewhere between 2.5% to 14% of shelter cats have heartworms at necropsy.[82] A nationwide antibody survey of more than 2000 largely asymptomatic cats revealed that nearly 12% of the cats had been host to third- or later-stage larvae;[46] it has been suggested that the real number is as high as 16%,[46] but other estimates have been lower (1%–8%).[47,94] If one uses a 12% antibody-positive rate as the national prevalence, and assume that 1% to 2% of cats will have mature heartworms in their pulmonary arteries and 5% to 6% of cats will develop signs after exposure consistent with HARD, then a nationwide feline morbidity might be expected to approach 6% to 8%. Also, based on owners' information, nearly one-third of cats diagnosed with heartworm disease at North Carolina State University were housed solely indoors.[90] The consequences of feline heartworm disease can be dire, and there are no standard therapeutic solutions. Therefore, having cats on a heartworm preventive regimen seems the prudent course.

Treatment in cats is currently problematic. Data on efficacy and safety of melarsomine against transplanted *D immitis* in cats are limited and contradictory.[92,95] In addition, the anecdotal clinical experience with melarsomine in naturally infected cats has been generally unfavorable, with an unacceptable mortality. Because of the inherent risk and lack of clear benefit, arsenical treatment is currently not recommended in cats.

Surgical removal of heartworms has been successful and is attractive because it minimizes the risk of thromboembolization.[96,97] The mortality seen in the only published case series was, unfortunately, unacceptable (two of five cats). Overall, the surgical approach still seems impractical for most cases.

Cats that are found to be infected with heartworms or that have heartworm disease should be placed on a monthly preventive and a short-term corticosteroid therapy (prednisone at 1 to 2 mg/kg from every 48 hours, up to two to three times a day) used to manage respiratory signs. If signs resolve initially but then recur, alternate-day steroid therapy (at the lowest dose that controls signs) can be continued indefinitely. Aspirin can be administered to cats with heartworm infections, but should not be prescribed with concurrent corticosteroid therapy.

Prognosis

The verdict is not yet in on heartworm disease in cats. More cats are getting infected than was previously considered; but the majority apparently goes through a period of disease, followed by self cure. However, some cats die unexpectedly and suddenly with heartworm-associated lesions. In cats with heartworm infections without clinical signs in Italy, of 43 infected cats 80% self-cured within 18

to 49 months (23 cats self-cured but had signs, 11 self-cured and never had signs).[36,83] Also, 3 cats died suddenly between 38 and 40 months after diagnosis, and at necropsy, were found to have two to three worms and severe thromboembolic processes.[82] Combining this and another Italian study, of 77 cats without signs seen in general practices in Italy only 58% eventually developed clinical heartworm disease, but of these cats one-third died of heartworm-related sequelae.[36,83] There is still no good and safe treatment for cats, and surgical removal is still in its infancy and may not be developed to any great extent if the outcome does not markedly improve in the cats so treated.

CONTROL RELATIVE TO ERADICATION OR DISEASE SUPPRESSION

Treatment

There are several excellent products to protect the well cared-for pet, but these methods are not suitable or easily applicable to mass treatment or long-term control in wildlife or dogs that are not under an owner's supervision.

Environmental

Mosquito control can have major effects on the transmission of mosquito-borne diseases, and has been shown numerous times with respect to the control of various human diseases such as Yellow fever, Dengue fever, and malaria. Mosquito control and abatement can and does have significant impact on these diseases in the United States and around the world. Dogs have very likely benefited greatly from the control of the mosquitoes that serve as vectors of disease and as major human pests in the United States. Fortunately for dogs, many of the most significant vectors of *D immitis* are also vectors of human disease. At the same time, due to the source of funding of the mosquito control programs, the targets of mosquito abatement programs are focused mainly on those species known to be important in human disease and comfort, and these might not be the same species affecting dogs. Thus, it is imperative that work be undertaken by different groups to maintain a dialog between the veterinary community and the mosquito control agencies to minimize the impacts of mosquito populations in any given area.

Wildlife

In the United States, the presence of the coyote makes heartworm eradication a difficult proposition. Coyotes are excellent and omnipresent reservoirs of the infection in rural, suburban, and now even urban parts of the country. Also, the existence of a wildlife reservoir raises the risk for heartworm infection of dogs, even if most dogs in a local area are protected and the local prevalence in well cared-for pets is low.

SUMMARY

Heartworm continues to be a parasite that threatens the canine population of the United States. *D immitis* causes significant morbidity and mortality in dogs, and is now found throughout the United States and in Canada along the United States border. The disease is transmitted by mosquitoes, including rural treehole mosquitoes like *Aedes sierrensis* and the urban *Aedes aegypti* and *Aedes albopictus*. The coyote is a known reservoir of infection and perpetuates heartworms even if all dogs in endemic areas are on preventive therapy. Excellent products to prevent heartworm infections in pets are available, and veterinarians need to be good stewards of their use. Because all the molecules used in the preventive products are from the same class of anthelmintic, veterinarians need to remain vigilant in monitoring heartworm infections in

dogs to verify that the emergence of worm populations that are refractory to the preventives does not occur, and if such infections do arise, an active approach needs to be taken to prevent their spread. Dogs that are receiving preventive treatments should be monitored annually to verify that the products are efficacious and that dogs receiving them are being protected. If infected dogs are found, they should be treated with an adulticide, then placed on a monthly preventive. Information on heartworm disease, its prevention and treatment in dogs and cats, new information on the disease, and news and updates can be found by contacting or visiting the websites of the American Heartworm Society (www.heartwormsociety.org) and the Companion Animal Parasite Council (www.capcvet.org).

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