Pathogenesis

The pathological, clinicopathological, and clinical response to infection with *D. immitis* in cats is not well understood. The pulmonary arterial response to adult heartworms is more severe than that of the dog, although pulmonary hypertension has infrequently been reported. Dillon demonstrated pulmonary enlargement within one week of transplantation of adults, suggesting an intense host-parasite interaction. A severe myointimal and eosinophilic response produces pulmonary vascular narrowing and tortuosity, thrombosis, and possibly hypertension. Because the feline pulmonary artery tree is smaller than that of the dog and has less collateral circulation, embolization, even with small numbers of worms, produces disastrous results with infarction and even death. Although uncommon, cor pulmonale and right heart failure can be associated with chronic feline HWI and is manifested by pleural effusion (hydro- or chylothorax) and/or ascites. The lung per se also is insulted by HWI, with eosinophilic infiltrates in the lung parenchyma (pneumonitis), pulmonary vasculature, and air spaces. The pulmonary vessels may leak plasma producing pulmonary edema, which has been considered by some to represent acute respiratory distress syndrome (ARDS). If the cat survives this initial insult, type II cells proliferate, replacing damaged type I cells, potentially impairing O2 diffusion. The end result is diminished pulmonary function, hypoxemia, dyspnea, and cough.

Acute or sudden death is typically associated with worm death and fulminant pulmonary failure, possibly associated with pulmonary embolism. Recent research suggests, however, an immune-mediated reaction to HW antigens in the feline shock organ (lung). Fatal respiratory failure probably results when HW antigen is released, producing bronchiolar and bronchial constriction, pulmonary congestion, superficial pulmonary hemorrhage, and periarterial hemorrhage.

“HARD”. It has been known since 1996 that cats exposed to heartworms but which reject maturation develop radiographic lesions. Recently, studies of both natural and experimental infections have confirmed this finding. In natural infections, pulmonary arterial lesions (myointimal proliferation and thrombotic obliteration) have been demonstrated in HW-free, antibody-positive cats and airway, pulmonary artery and pulmonary interstitial lesions have been demonstrated in cats heavily, experimentally-infected cats in which pharmacological abortion of the infection at the early L5 stage was performed. This combination of data from experimental and natural infections indicates that when cats abort infections at the early 5th stage, radiographic and histological changes develop in the lungs, likely producing the most commonly recognized signs in cats, cough, dyspnea and wheezing. The American Heartworm Society has utilized this information in a campaign for heartworm awareness, labeling it “HARD” or “Heartworm-Associated Respiratory Disease”. The fact that immature adults that never fully mature can cause disease is important to our understanding of this syndrome. We do not know if the resultant pathology is persistent, whether it can result in fatality, and if it explains signs later in the disease course. It also causes confusion as to the exact terminology for HWI as a cat may fall outside the standard concept of “exposed and uninfected” as opposed to “infected”.

A symbiotic bacterium, *Wolbachia*, is known to occur within filarial parasites at all stages. This bacterium is essential for filarial reproduction and well-being. It has been hypothesized that antigens from these bacteria are proinflammatory, contributing to the HWD, particularly upon the death of the adult HW and that, possibly, treatment of bacteria with tetracycline might be a strategy in the treatment adult dirofilariasis. Currently, there are no data to support this interesting hypothesis. However, doxycycline coupled with ivermectin has proven beneficial in HW-infected dogs.
Clinical Signs

Cats with HWI may be asymptomatic and, when present, clinical manifestations may be either peracute/acute or chronic. Acute or peracute presentation is usually due to worm death, embolization or aberrant migration and signs variably include salivation, tachycardia, shock, dyspnea, hemoptysis, vomiting and diarrhea, syncope, dementia, ataxia, circling, head tilt, blindness, seizures, and death. More commonly, the onset of signs is less acute (chronic form). Reported historical findings in chronic feline HWD include anorexia, weight loss, lethargy, exercise intolerance, signs of right heart failure (pleural effusion; rare), cough, dyspnea, and vomiting. We have found dyspnea and cough to be relatively consistent findings and, when present, should cause suspicion of HWD in endemic areas.

In a report of 50 natural cases of feline HWI seen at North Carolina State University, presenting signs were most commonly related to the respiratory system (32 cats; 64%), with dyspnea (24 cats; 48%) being most often noted, followed by cough (19 cats; 38%), and wheezing. Vomiting was reported in 17 (38%) cats and was noted frequently in 8 (16%). Five (10%) heartworm-infected cats were reported to have exhibited vomiting without concurrent respiratory signs and vomiting was a presenting sign in 7 (14%). Neurological signs (including collapse or syncope, which were described in 5 [10%]) were reported in 7 (14%) cats. Five (10%) of the cats were dead at the time of presentation. Murmurs were infrequently noted in cats that did not have concurrent heart disease, independent of heartworm infection. Heart failure was present in 1 cat but this cat had concurrent hypertrophic cardiomyopathy. Heartworm infection was considered to be an incidental finding in 14 (28%) of the cats in this study. Physical examination is often unrewarding although a murmur, gallop, and/or diminished or adventitial lung sounds may be audible. In addition, cats may be thin and/or dyspneic. If heart failure is present, jugular venous distension, dyspnea, and rarely ascites may be detected.

Treatment

The use of arsenical-adulticides is problematic. Thiacetarsemide, if available, poses risks even in normal cats. Turner and colleagues reported death due to pulmonary edema and respiratory failure in 3 of 14 normal cats given of thiacetarsemide (2.2 mg/kg twice over 24 hours). Dillon could not confirm this acute pulmonary reaction in 12 normal cats receiving thiacetarsemide, but 1 cat did die after the final injection. More importantly, a significant, though unquantified, percentage of cats with HWI develop pulmonary thromboembolism after adulticidal therapy. This occurs several days to a week after therapy and is often fatal. In 50 cats with HWI, seen at North Carolina State University, 11 received thiacetarsemide. There was no significant difference in survival between those receiving thiacetarsemide and those receiving symptomatic therapy.

Data on melarsomine in experimental (transplanted) HWI in cats are limited and contradictory. Although there is an abstract report in which 1 injection (2.5 mg/kg; ½ the recommended canine dosage) of melarsomine was used in experimentally-infected cats without treatment related mortality, the worm burdens after treatment were not significantly different than those found in untreated control cats. Diarrhea and heart murmurs were frequently noted in treated cats. A second abstract report, using either the standard canine protocol (2.5 mg/kg twice over 24 hours) or the “split-dosage” (1 injection, followed by 2 injections, 24 hours apart, in 1 month), gave more favorable results. The standard treatment and split-dosage regimens resulted in 79% and 86% reduction in worm burdens, respectively and there were no adverse reactions. Although promising, these unpublished data need to be interpreted with caution as the transplanted worms were young (<8 months-old and more susceptible), the cats may not have had time to develop antibodies to HW antigens, thereby reducing the risk of anaphylaxis, and the control cats experienced a 53% worm mortality (average worm burden was reduced by 53% by the act of transplantation). Additionally, the clinical experience in naturally-infected cats has been generally unfavorable, with an unacceptable mortality. Because of the inherent risk, lack of clear benefit, and the short life expectancy of heartworms in this species, this author does
not advocate adulticidal therapy in cats. Surgical removal of heartworms has been successful and is attractive because it minimizes the risk of thromboemboli. The mortality in one case series, using a urethral stone basket, was, unfortunately, unacceptable (2 of 5 cats). We have reported success in cats with heartworm disease due to HW, retrieving worms with the nitinol snare, using fluoroscopic guidance. This procedure holds promise for the future.

Cats with HWI should be placed on a monthly preventative and short-term corticosteroid therapy (prednisone at 1-2 mg/kg q48h-tid) used to manage respiratory signs. If signs recur, alternate day steroid therapy (at the lowest dosage that controls signs) can be continued indefinitely. For respiratory emergencies, oxygen, corticosteroids (dexamethasone at 1 mg/kg IV or IM or prednisolone sodium succinate at 50-100 mg IV/cat) and bronchodilators (aminophylline at 6.6 mg/kg IM q12h, theophylline sustained release at 10 mg/kg PO or terbutaline at 0.01 mg/kg SC) may be employed. Bronchodilators have logic, based on the ability of agents, such as the xanthines (aminophylline and theophylline), to improve function of fatigued respiratory muscles. In addition, the finding of hyperinflation of lung fields may indicate bronchoconstriction, a condition for which bronchodilators would be indicated. Nevertheless, this author does not routinely utilize bronchodilators in feline HWI.

Recently, doxycycline (10 mg/kg q12h for 30 days) has been used to clear Wolbachia from heartworm-infected dogs to reduce embolic complications, reduce microfilaria numbers more rapidly, and to hasten macrocyclic lactone-induced HW death (“slow-, soft- or trickle-kill”). There are no published studies to indicate that the use of doxycycline in should become routine practice in the management of HWI in cats. In fact, some feel that anything that shortens the life expectancy of the parasite is most likely harmful to the cat. Alternatively, the gradual destruction of the heartworm, associated with loss of the symbiotic bacteria, appears to lessen the response to dying worms, when coupled with ivermectin in dogs with HWI.

The use of aspirin has been questioned as vascular changes associated with HWI consume platelets, increasing their turnover rate and effectually diminishing the antithrombotic effects of the drug. Conventional doses of aspirin did not prevent angiographically-detected vascular lesions. Dosages of aspirin necessary to produce even limited histological benefit approached the toxic range. However, because therapeutic options are limited; because at conventional doses (40 - 80 mg PO q72h), aspirin is generally harmless, inexpensive, and convenient; and because the quoted studies were based on relatively insensitive estimates of platelet function and pulmonary arterial disease (thereby possibly missing subtle benefits), the author continues to advocate aspirin for asymptomatic cats with HWI. Aspirin is not prescribed with concurrent corticosteroid therapy. Since the vast majority of cats are amicrofilaremic, microfilaricidal therapy is unnecessary in this species. Management of other signs of HW in cats is largely symptomatic.

Prognosis
In the aforementioned study of 50 cats with natural heartworm infection, at least 12 cats died of causes other than heartworm disease. Seven of these and 2 living cats were considered to have survived heartworm disease (lived >1000 days). The median survival for all heartworm-infected, cats living beyond the day of diagnosis, was 1460 days (4 years; range 2-4015 days), while the median survival of all cats (n=48 with adequate follow-up) was 540 days (1.5 years; range 0-4015 days). Survival of 11 cats treated with sodium caparsolate (mean 1669 days) was not significantly different from that of the 30 managed without adulticide (mean 1107 days). Likewise, youth (< 3 years of age), presence of dyspnea, cough, ELISA-positivity for heartworm antigen, presence of echocardiographically-identifiably worms, or gender of the cat did not appear to affect survival. The effect of HWI on survival has been compared to that of other cardiovascular diseases. Overall, the prognosis for HWI in cats is comparable to that of hypertrophic cardiomyopathy, the most benign of primary feline heart diseases.