

CHAPTER 49

MYOCARDITIS

Meg Sleeper, VMD, DACVIM (Cardiology)

KEY POINTS

- Myocarditis is an inflammatory process involving the heart. Inflammation may involve the myocytes, interstitium, or vascular tree.
- Myocarditis has been associated with a wide variety of diseases. Infectious agents (viral, bacterial, protozoal) may cause myocardial damage by myocardial invasion, production of myocardial toxins, or activation of immune-mediated disease.
- Myocarditis can also be associated with physical agents (doxorubicin), underlying metabolic disorders (uremia), toxins (heavy metals), or physical agents (heat stroke).

Myocarditis is a rare cause of heart failure in dogs and cats. Clinical features vary, including those of asymptomatic patients who may have electrocardiographic abnormalities and patients with or without heart enlargement, systolic dysfunction, or even full-blown congestive heart failure (CHF). The patient's history (i.e., environment and exposure) is often critical in determining likely risk and suggesting appropriate diagnostic tests. Clinical reports of canine myocarditis are most common in immunocompromised or immunonaïve patients.

INFECTIOUS MYOCARDITIS

Viral Myocarditis

Numerous viruses have been associated with myocarditis in humans. In dogs, viral myocarditis appears most commonly in immunonaïve patients, and the virus most commonly associated with the disease is parvovirus. However, at this time the entity appears to be very rare. In the late 1970s and early 1980s, when the parvovirus pandemic first was recognized, puppies did not receive maternal antibodies and very young puppies developed a fulminant infection with acute death as a result of pulmonary edema when exposed to the virus. Older puppies (2 to 4 months) often died subacutely from CHF, but others developed a milder myocarditis and later developed dilated cardiomyopathy (DCM), usually as young adults. Basophilic

intranuclear inclusion bodies are found in the myocardium of acutely affected younger puppies but may be absent in older puppies.¹ Older dogs typically have gross myocardial scarring. Rare cases of parvovirus-induced myocarditis have been reported since the early to mid-1980s.

Rarely other viruses have been associated with myocarditis in dogs. In 2001 Maxson and others evaluated myocardial tissue from 18 dogs with an antemortem diagnosis of DCM and 9 dogs with a histopathologic diagnosis of myocarditis based on a polymerase chain reaction analysis to screen for canine parvovirus, adenovirus types 1 and 2, and herpesvirus. Canine adenovirus type 1 was amplified from myocardium of only one dog with DCM and none of the dogs with myocarditis, suggesting these pathogens are not commonly associated with DCM or active myocarditis in the dog.² Distemper virus–associated cardiomyopathy with a mild inflammatory infiltrate has been produced by experimental infection of immunonaïve puppies.³ Natural infection with West Nile virus was associated with myocarditis in a wolf and a dog in 2002, the third season of the West Nile virus epidemic in the United States.⁴ Viral genomic deoxyribonucleic acid has also been identified in feline myocardial tissue from patients with hypertrophic cardiomyopathy, DCM, and restrictive cardiomyopathy, suggesting that viral myocarditis may be a factor in these feline-acquired diseases.¹

Protozoal Myocarditis Chagas' disease

Chagas' disease is caused by *Trypanosoma cruzi*, a protozoal parasite. Chagas' disease is the leading cause of DCM in humans of Latin America, but it is rare in North America. In North American dogs, Chagas' disease occurs most commonly in Texas and Louisiana. There have been no reported feline cases in North America. The organism is transmitted by an insect vector (Reduviidae), and reservoir hosts include rodents, raccoons, opossums, dogs, cats, and humans. The trypomastigote is the infective stage, but on entering host cells the organism enters the reproductive stage and becomes an amastigote. Amastigotes multiply until the host cell ruptures.^{1,5}

Dogs with clinical Chagas' disease have an acute or a chronic syndrome. In the acute stage, circulating trypomastigotes may be seen in a thick blood smear, and most dogs are brought for treatment

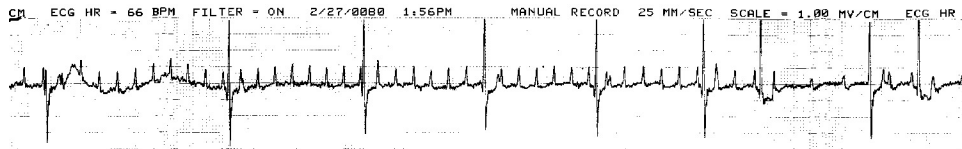


FIGURE 49-1 Electrocardiogram from a mixed breed dog with trichinosis involving the heart. The dog was brought in for collapse caused by complex arrhythmias. Note the ventricular escape beats. An underlying supraventricular tachycardia is likely as well.

because of sudden development of signs of right-sided heart failure (ascites, tachycardia, lethargy). Dogs with chronic Chagas' disease may enter a quiescent stage free of clinical signs for months or even years. Nervous system damage often causes ataxia and weakness in these patients.^{1,5}

Bacterial and Other Causes of Myocarditis

Bacterial myocarditis is possible whenever bacteremia or sepsis is present, with the most common agents being staphylococcal and streptococcal species.¹ Myocarditis associated with *Citrobacter koseri*, an opportunistic pathogen of immunosuppressed human patients, has been described in two 12-week-old sibling Boxer puppies.⁶ Tyzzer's disease (infection with *Bacillus piliformis*) was associated with severe necrotizing myocarditis in a wolf-dog hybrid puppy.⁷ Two cases of feline *Streptococcus canis* myocarditis have been reported.^{8,9}

Myocarditis has also been recognized secondary to rickettsial organisms such as *Rickettsia rickettsii*, *Ehrlichia canis*, and various *Bartonella* species.¹ Myocarditis has been noted in 2 of 12 dogs diagnosed with endocarditis, 11 of which were seroreactive to *Bartonella vinsonii* subspecies.¹⁰ Lymphoplasmacytic myocarditis was observed in 8 cats experimentally infected with *Bartonella*; however, clinical signs consistent with heart disease were not observed.¹¹ *Bartonellae* have been implicated as an important cause of endocarditis in humans and dogs. Recently the organism has also been linked to endocarditis in the cat, and a few case reports suggest cats may develop myocarditis associated with *Bartonellae* as well.^{12,13} Lyme disease (secondary to infection by the spirochete *Borrelia burgdorferi*) has been implicated as a cause of myocarditis in dogs, but documented cases are rare. Clinical signs are often vague and nonspecific, and serologic testing is not a reliable method to determine active infection.¹ In humans, Lyme myocarditis may be due to direct toxic effects or immunomediated mechanisms, and the disease is usually self-limiting.¹⁴ Fungal infections of the myocardium are extremely rare but have occurred in immunocompromised patients.¹

A group of cats was described with transient fever and depression that appeared to be infectious in nature. Postmortem examination revealed microscopic lesions consistent with myonecrosis and an inflammatory cell infiltrate. A viral etiology was suspected, but no organism was identified.⁸ In a retrospective study reviewing 1472 feline necropsies over a 7-year period, 37 cases were diagnosed with endomyocarditis. The cats with endomyocarditis had a mean age at death of 3.4 years, and 62% of them had a history of a stressful event 5 to 10 days before being brought for treatment. Interstitial pneumonia was present in 77% of the cats at postmortem examination. Special stains for bacteria and fungi were negative.¹⁵

Parasitic agents can also lead to myocarditis. *Toxoplasma gondii* bradyzoites can encyst in the myocardium, resulting in chronic infection. Eventually the cysts rupture, leading to myocardial necrosis and hypersensitivity reactions.¹ Toxoplasmosis has been reported to be a cause of myocarditis in cats.¹⁶ *Neospora caninum* can infect multiple tissues, including the heart, peripheral muscles, and central nervous system. Clinical signs associated with noncardiac tissues typically predominate; however, collapse and sudden death has been reported in affected dogs.¹ Infestation with *Trichinella spiralis* is a common

BOX 49-1 Characteristics Suggestive of Myocarditis

- History suggests it is possible (e.g., oncology patient receiving doxorubicin, dog lives in Texas)
- Unusual signalment for heart disease (e.g., Irish Setter, German Shepherd)
- Supportive electrocardiographic findings include conduction abnormalities or arrhythmias
- Supportive echocardiographic findings include myocardial dysfunction (which may be regional) with or without heart enlargement
- Supportive clinical laboratory findings include leukocytosis, eosinophilia, elevated cardiac troponin I levels

cause of mild myocarditis in humans.¹⁴ The parasite has been associated with at least one case of canine myocarditis complicated by arrhythmias (Figure 49-1).¹⁷

NONINFECTIOUS MYOCARDITIS

Doxorubicin Toxicity

Doxorubicin cardiotoxicity may be manifested as arrhythmias, myocardial failure, or both. Cardiotoxicity is dosage dependent and irreversible and is more common at cumulative doses exceeding 250 mg/m²; however, in one study in which only two doses of 30 mg/m² were administered, 3% of dogs developed cardiomyopathy.^{1,8} The time to onset of CHF in affected dogs is highly variable. Although pathologic changes have been seen in the feline myocardium after administration, no antemortem echocardiographic or electrocardiographic changes associated with doxorubicin toxicity have been reported.

Other causes of noninfectious myocarditis, although rarely recognized in veterinary medicine, include allergic reactions, systemic diseases such as vasculitis, and physical agents such as radiation or heat stroke.¹⁴ Numerous chemicals and drugs may lead to cardiac damage and dysfunction. A severe reversible DCM has been observed in humans with pheochromocytoma,¹⁴ and similar findings have been observed in experimental animals receiving prolonged infusions of norepinephrine.¹⁴ Myocardial coagulative necrosis was found in a dog that died suddenly after an episode of severe aggression, restraint, and sedation for grooming.¹⁸ Myocardial lesions were presumed to be caused by catecholamine toxicity. A canine case of immune-mediated polymyositis with cardiac involvement has also been reported.¹⁹

DIAGNOSIS

Definitive diagnosis, unless the history clearly suggests myocarditis (e.g., doxorubicin toxicity), is elusive (Box 49-1). Supportive clinical laboratory tests include leukocytosis or eosinophilia, particularly in parasitic or allergic myocarditis. Elevated cardiac troponin I levels provide evidence of myocardial cell damage in patients suspected of having myocarditis. If a high suspicion for Chagas' disease is present,



FIGURE 49-2 Photograph showing a bioptome used for endomyocardial biopsies via intravascular access.

serologic examination for *T. cruzi* is diagnostic. Demonstration of a rising titer is also helpful to establish the diagnosis of myocarditis associated with *T. gondii* or *N. caninum*. Viral and rickettsial testing should be performed if indicated. Blood cultures should be performed if a bacterial cause is suspected. Thoracic radiographs may show normal heart size or heart enlargement with or without evidence of CHF. The electrocardiographic findings may also be varied, and ventricular arrhythmias or conduction disturbances are common. Echocardiography most often demonstrates systolic dysfunction, either global or regional, and cardiac chambers may be normal or increased in size.

Endomyocardial biopsy (the gold standard for diagnosis of myocarditis in humans²⁰) may allow definitive antemortem diagnosis (Figure 49-2). However, a focal myocarditis can still be missed because the sample size is small. At postmortem examination, immunohistochemistry or electron microscopy can confirm the diagnosis of *N. caninum* infection.²¹ Gross pathology findings may be insignificant, or they may reveal cardiac dilation or ventricular hypertrophy, focal petechiae, and myocardial abscesses.¹ Specific findings depend on the underlying etiology. Focal or diffuse myocarditis is definitively diagnosed by histopathology when myocyte necrosis, degeneration, or both are associated with an inflammatory infiltrate.¹

TREATMENT

Most recommendations for managing myocarditis in dogs and cats are extrapolated from human medicine or research with models of viral myocarditis. Supportive care is the first line of therapy for patients with myocarditis. In those patients with signs of CHF, typical therapy should include preload reduction with diuretics and afterload reduction with angiotensin-converting enzyme inhibitors (see Chapter 40). Digoxin increased expression of proinflammatory cytokines and increased mortality in experimental myocarditis, so it is recommended to be used with caution and at low dosages.²⁰ Intravenous inotropic therapy in the form of dobutamine can be useful if significant systolic dysfunction is present. Alternatively, pimobendan may be beneficial to address systolic dysfunction and reduce afterload.

Eliminating unnecessary medications may help reduce the possibility of allergic myocarditis. Results of recent studies suggest that immunosuppression is not routinely helpful in myocarditis patients, but it may have an important role in patients with myocardial dysfunction caused by systemic autoimmune disease.²⁰ Nonsteroidal antiinflammatory agents are contraindicated during the acute phase

of myocarditis in humans (during the first 2 weeks) because they increase myocardial damage. However, they appear to be safe later in the course of disease.¹⁴ In a murine model of viral myocarditis, angiotensin-converting enzyme inhibition (with captopril) was beneficial. Similarly, interferon therapy is beneficial in the experimental model of myocarditis and may be useful clinically.¹⁴

When diagnosis of acute Chagas' disease is possible, several agents appear to inhibit *T. cruzi*; however, by the time a diagnosis is made it is often too late for this approach. Patients with chronic Chagas' disease are treated symptomatically for CHF. Similarly, successful treatment has been reported using several agents in dogs affected with *N. caninum* myocarditis, but severely ill dogs often die.¹ Clindamycin is the drug of choice for treating clinical toxoplasmosis in dogs and cats; however, significant damage to the heart is irreversible.²¹ In one report of a cat with presumed toxoplasmosis, signs of heart disease did resolve with clindamycin treatment.²²

Dogs with evidence of bacteremia should be treated with antibiotics pending culture and susceptibility results. Empiric treatment should be effective against staphylococcal and streptococcal species (see Chapter 93). Animals with suspected rickettsial disease should be treated with doxycycline (5 to 10 mg/kg PO or IV q12-24h) pending titer results.

REFERENCES

1. Fox PR, Sisson DK, Moise NS, editors: Textbook of canine and feline cardiology: principles and clinical practice, ed 2, St Louis, 1999, WB Saunders.
2. Maxson TR, Meurs KM, Lehmkuhl LB, et al: Polymerase chain reaction analysis for viruses in paraffin-embedded myocardium from dogs with dilated cardiomyopathy or myocarditis, *Am J Vet Res* 62:130, 2001.
3. Higgins RJ, Krakowka S, Metzler AE, et al: Canine distemper virus-associated cardiac necrosis in the dog, *Vet Pathol* 18:472, 1981.
4. Lichtensteiger CA, Heinz-Taheny K, Osborne TS, et al: West Nile virus encephalitis and myocarditis in a wolf and dog, *Emerg Infect Dis* 9:1303, 2003.
5. Kittleson MD: Primary myocardial disease leading to chronic myocardial (dilated cardiomyopathy) and other related diseases. In Kittleson MD, Kienle RD: Small animal cardiovascular medicine, ed 1, St Louis, 1998, Mosby.
6. Cassidey JP, Callanan JJ, McCarthy G, et al: Myocarditis in sibling Boxer puppies associated with *Citrobacter koseri* infection, *Vet Pathol* 39:393, 2002.
7. Young JK, Baker DC, Burney DP: Naturally occurring Tyzzer's disease in a puppy, *Vet Pathol* 32:63, 1995.
8. Sura R, Hinckley LS, Risatti GR, et al: Fatal necrotizing fasciitis and myositis in cat associated with *Streptococcus canis*, *Vet Rec* 162:450, 2008.
9. Matsuo A, Kanda T, Sugiyama A, et al: Mitral stenosis with bacterial myocarditis in a cat, *J Vet Med Sci* 69:1171, 2007.
10. Breitschwerdt EB, Atkins CE, Brown TT, et al: *Bartonella vinsonii* subsp *berkhoffii* and related members of the alpha subdivision of the proteobacteria in dogs with cardiac arrhythmias, endocarditis or myocarditis, *J Clin Microbiol* 37:3618, 1999.
11. Kordick DL, Brown TT, Shin K, et al: Clinical and pathologic evaluation of chronic *Bartonella henselae* or *Bartonella clarridgeiae* infection in cats, *J Clin Microbiol* 37:1536, 1999.
12. Nakamura RK, Zimmerman SA, Lesser MB: Suspected *Bartonella*-associated myocarditis and supraventricular tachycardia in a cat, *J Vet Cardiol* 13:277, 2011.
13. Varanat M, Broadhurst J, Linder KE, et al: Identification of *Bartonella henselae* in 2 cats with pyogranulomatous myocarditis and diaphragmatic myositis. *Vet Pathology* 2012;49:608-61.
14. Wynne JA, Braunwald E: The cardiomyopathies and myocarditides. In Braunwald E, Zipes DP, Libby P, Bonow RO, editors: Braunwald's heart disease: a textbook of cardiovascular medicine, ed 7, Philadelphia, 2005, Saunders.
15. Stalis IH, Bossbaly MJ, Van Winkle TJ: Feline endomyocarditis and left ventricular endocardial fibrosis, *Vet Pathol* 32:122, 1999.

16. Dubey JP, Carpenter JL: Histologically confirmed clinical toxoplasmosis in cats: 100 cases (1952-1990), *J Am Vet Med Assoc* 203:1556, 1993.
17. Sleeper MM, Bissett S, Craig L: Canine trichinosis presenting with high grade second degree AV block, *J Vet Intern Med* 20:1228, 2006.
18. Pinson DM: Myocardial necrosis and sudden death after an episode of aggressive behavior in a dog, *J Am Vet Med Assoc* 211:1371, 1997.
19. Warman S, Pearson G, Barret E, et al: Dilation of the right atrium in a dog with polymyositis and myocarditis, *J Small Anim Pract* 49:302, 2008.
20. Feldman AM, McNamara D: Myocarditis, *N Engl J Med* 343:1388, 2000.
21. Dubey JP, Lappin MR: Toxoplasmosis and neosporosis. In Green CE, editor: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, WB Saunders.
22. Simpson KE, Devine BC, Funn-Moore D: Suspected toxoplasmosis-associated myocarditis in a cat, *J Fel Med Surg* 7:203, 2005.