

Ferret Cardiology



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KEYWORDS

- Arrhythmia • Cardiomyopathy • Cardiac disease • Dirofilariosis • Echocardiography
- Electrocardiography • *Mustela putorius furo* • Valvular disease

KEY POINTS

- Cardiac disease is seen most often in middle-aged to older ferrets, with dilated cardiomyopathy and endocardiosis being the most common cardiac abnormalities to be diagnosed.
- Clinical signs are often recognized only in advanced stages of disease and may involve signs of congestion (eg, pleural effusion, respiratory distress, and/or ascites) or decreased cardiac output (eg, hind limb weakness, syncope, exercise intolerance).
- Diagnostic workup will usually involve (a combination of) echocardiography, electrocardiography, and/or radiographs, with the method of choice being dependent on the type of clinical signs presented by the ferret.
- Therapeutic options and dosing regimen largely follow guidelines such as those established in dogs and cats and are aimed at alleviating sign of congestion, improving cardiac output, and reducing preload and afterload.

INTRODUCTION

Cardiac disease is relatively common in pet ferrets, particularly in middle-aged to older ferrets, and may comprise either problems with conduction, contractility, or outflow.¹⁻⁴ These problems may arise from anatomic and/or physiologic disorders of varying causes.

In practice, ferrets are more commonly presented with heart failure, which is the end result of severe (systolic and/or diastolic) cardiac dysfunction and *only* occurs when severe cardiac disease is present. Resulting clinical signs arise either from increased venous pressure and congestion (ie, *backward failure*) or from low cardiac output and poor tissue perfusion (ie, *forward failure*). Less frequently, ferrets are diagnosed with cardiac disease in the absence of heart failure, which, dependent on the condition, may or may not require therapy, and may or may not ever progress to heart failure.^{1,4}

To work up a cardiac ferret case in practice, knowledge of the diagnostic and therapeutic options as well as the cardiac diseases/conditions themselves is needed. This

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article provides an overview of the diagnostic tools and treatment options, and different cardiac conditions reported in ferrets, including specifics regarding their diagnosis, treatment, and outcome.

DIAGNOSING CARDIAC DISEASE

Physical Examination

Clinical signs in ferrets with heart disease are often nonspecific and may include lethargy, exercise intolerance, weight loss, and anorexia. Other signs include tachypnea, cough (albeit rare), weakness in the hind limbs, and syncope (the latter specifically in bradyarrhythmic animals).^{1,3,4}

During the physical examination, special attention should be paid to the heart, arterial, venous, and capillary systems. As a result of reduced output, mucous membranes can become pale or cyanotic, with a prolonged capillary refill time (CRT; **Fig. 1**).^{3,4} In addition, a weak or irregular pulse may be palpated (**Fig. 2**). Auscultation of the heart is performed between the sixth and eighth intercostal space to evaluate whether heart murmurs, bradycardia, tachycardia, arrhythmias, or muffled heart sounds is present (**Fig. 3**).⁵ Lungs should also be auscultated to evaluate the presence of moist rales or crackles, muffled lung sounds, or increased bronchovesicular sounds, indicative of pleural effusion or lung edema.^{1,4} Venous tension cannot easily be determined in ferrets. The abdomen should be checked for the presence of ascites, though.

Diagnostic Workup

To diagnose cardiac disease, an echocardiogram, thoracic radiographs, electrocardiogram (ECG), blood pressure measurement, blood work (complete blood count + biochemical profile), and/or urinalysis may be required. In areas where heartworm (*Dirofilaria immitis*) is endemic, specific testing is indicated. Thoracocentesis or abdominocentesis can be performed when fluid is present. This will not only provide material for cytologic, biochemical, and/or bacteriologic examination but also alleviate the associated dyspnea and discomfort.^{1,3,4}

Findings obtained during the physical examination will largely determine which diagnostic test to pursue. For example, when abnormal sounds are auscultated, an echocardiogram is the first-choice diagnostic technique, whereas ECG is most useful when an abnormal rhythm or pulse frequency is detected. In the case of coughing, tachypnea, and/or dyspnea, the radiograph will be the method of choice, followed by an echocardiogram in the case of pleural effusion or heart enlargement.⁴



Fig. 1. In ferrets, CRT can most easily be determined on the unimpigmented foot pads.



Fig. 2. In ferrets, the femoral pulse is easiest to palpate while the ferret's body rests on the forearm of the examiner.

Echocardiography

Echocardiography is ideal for identifying structural and/or functional abnormalities of the heart.^{6,7} Sedation is often preferred to be able to perform accurate measurements and obtain accurate M-mode registrations and color-flow Doppler examinations (**Fig. 4**).

The routine echocardiogram (B-mode) is performed with the ferret in right and left lateral recumbency using imaging planes similar to those obtained in other species. Reference ranges for common cardiac measurements are summarized in **Table 1**. During the examination, the cardiac size is assessed, as well as contractility of the heart and leakage of the valves. M-mode measurements and Doppler echocardiography provide information on chamber dimensions, wall thickness, and systolic function, and blood flow velocity, and turbulence (indicative of, eg, valvular regurgitation), respectively (**Fig. 5**). Ultrasonography may also reveal the presence of effusion in the pericardium, thorax, or abdomen, as well as hepatomegaly or splenomegaly owing to congestion.⁷

Radiography

Thoracic radiographs are useful to detect lung edema or pleural effusion (signs of congestive heart failure; **Fig. 6**). The best-positioned, standard 2-view thoracic radiographs are often obtained in the sedated or anesthetized animal. However, sedation



Fig. 3. In ferrets, because of the more caudal position of the heart, auscultation is performed at the level of the sixth to eighth intercostal space.



Fig. 4. Ferrets frequently are so mobile that performing a proper echocardiography is not possible without sedation. For this purpose, the use of short-acting injectables and/or inhalant anesthetics is recommended. Just as in the other companion animals, ultrasound should best be performed on both sides of the thorax. However, in the case of severe dyspnea, it may be best to place the ferret in sternal recumbency.

can decrease the inspiratory volume, thereby hindering accurate evaluation of the lungs.⁴

The heart size is evaluated using a modified vertebral heart score, for which different methods exist.⁹ However, if the heart size is increased, these methods do not allow for distinction between pericardial effusion or cardiomegaly nor the type of cardiomegaly (dilated or hypertrophic cardiomyopathy) leading to the size increase. Echocardiography therefore remains the preferred diagnostic tool for evaluating cardiac disease.

Electrocardiography

ECGs are predominantly used in ferrets suspected of an abnormal heart rate or rhythm.^{7,10–12} As electrical conduction is altered in the case of cardiac chamber

Parameter	Mean ± SD	Range	Median
IVSd (mm)	3.4 ± 0.4	2.5–4.4	3.4
IVSs (mm)	4.4 ± 0.6	3.3–5.4	4.4
LVIDd (mm)	9.8 ± 1.4	6.8–12.7	9.6
LVIDs (mm)	6.9 ± 1.3	4.5–9.7	6.9
LVWd (mm)	2.7 ± 0.5	1.8–3.7	2.7
LVWs (mm)	3.8 ± 0.8	2.4–5.9	3.8
FS (%)	29.5 ± 7.9	13.9–48.7	28.0
Ao (mm)	4.4 ± 0.6	3.3–6.0	4.2
LAAD (mm)	5.8 ± 0.9	3.2–7.3	5.7
LAAD/Ao	1.3 ± 0.2	1.0–1.8	1.3
EPSS (mm)	1.2 ± 0.6	0–2.2	1.2

Abbreviations: Ao, aorta diameter; EPSS, E-point to septal separation diameter; FS, fractional shortening; IVSd and IVSs, interventricular septum thickness in diastole and systole; LAAD, left atrium appendage diameter; LVIDd and LVIDs, left ventricular internal diameter in diastole and systole; LVWd and LVWs, left ventricular wall thickness in diastole and systole; SD, standard deviation.

(Derived from Vastenburg et al, 2004).⁸

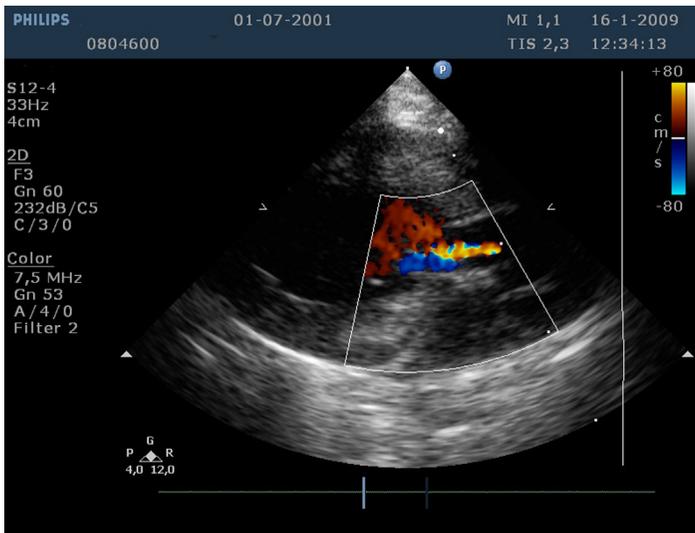


Fig. 5. Color-flow Doppler can be used to assess the velocity of the blood flow and potential presence of turbulence, indicative of, for example, valvular regurgitation. Flow toward the transducer is depicted in red, whereas flow away from the transducer is shown in blue. In the case of turbulent flow, both colors are mixed, as can be seen in this ferret with an aorta valve insufficiency.

enlargement, pericardial and/or pleural effusion, ECGs can be helpful for the diagnosis of these conditions. In addition, ECGs can be indicated for monitoring the progression of cardiac disease and effects of cardioactive drugs, or for monitoring cardiac function during anesthesia.⁷

Physiologic and pathologic arrhythmias that have been identified in ferrets include sinus bradycardia and tachycardia, atrial and ventricular premature contractions, atrial fibrillation, first-, second-, and third-degree atrioventricular (AV) blocks.

Bradycardia or bradyarrhythmia can be due to metabolic causes (eg, hypokalemia or hyperkalemia, hypoglycemia) and may be vagally mediated. A so-called atropine

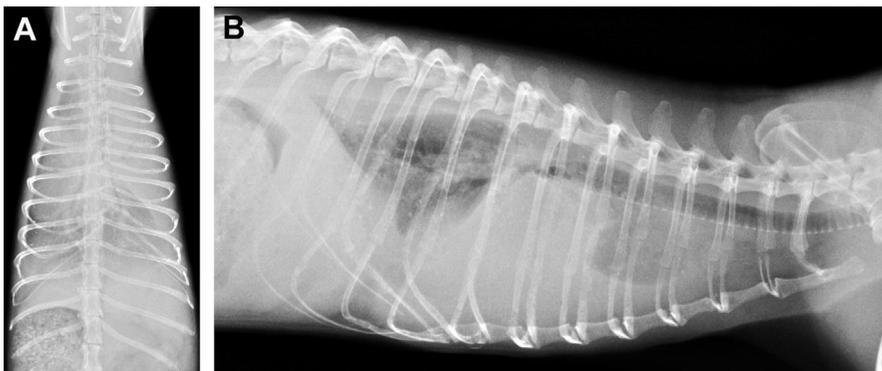


Fig. 6. Dorsoventral (A) and lateral (B) radiographs of a ferret with severe pleural effusion. Fluid accumulation obscures the heart shadow and compresses the lungs, which, similar to the trachea, show up as radiolucent structures dorsal in the thorax, owing to the presence of air.

response test, during which atropine is administered intravenously (IV), intramuscularly (IM), or subcutaneously (SC) at 0.02 to 0.05 mg/kg, can be performed to evaluate vagal involvement.⁴ In vagally mediated bradycardia, increased heart rates or improved SA and AV node conduction can be within 15 to 30 minutes following atropine administration (Fig. 7). Incomplete responses may necessitate a repetition of the procedure.

Electrocardiogram Interpretation

ECG interpretation is done according to a standardized protocol:

1. Calculate the heart rate (in beats per minute, bpm) by counting the number of QRS complexes over a length of 7.5 cm (equaling 3 seconds) at a paper speed of 25 mm/s and multiply the number of complexes by 20.
2. Assess the heart rhythm through evaluation of the following parameters:
 - a. Regularity of the rhythm, when marking 4 R waves on a piece of paper, the marks should continue to correspond to any and all R waves upon moving the paper with markings alongside the ECG (a variation of 10% in regularity is considered acceptable);
 - b. Presence, configuration, uniformity, and regularity of the P waves;
 - c. Presence, configuration, uniformity, and regularity of the QRS complexes;
 - d. Presence of a relationship between P waves and following QRS complexes: evaluate (a) whether each P wave is followed by a QRS complex; and (b) whether each QRS complex is preceded by a P wave.

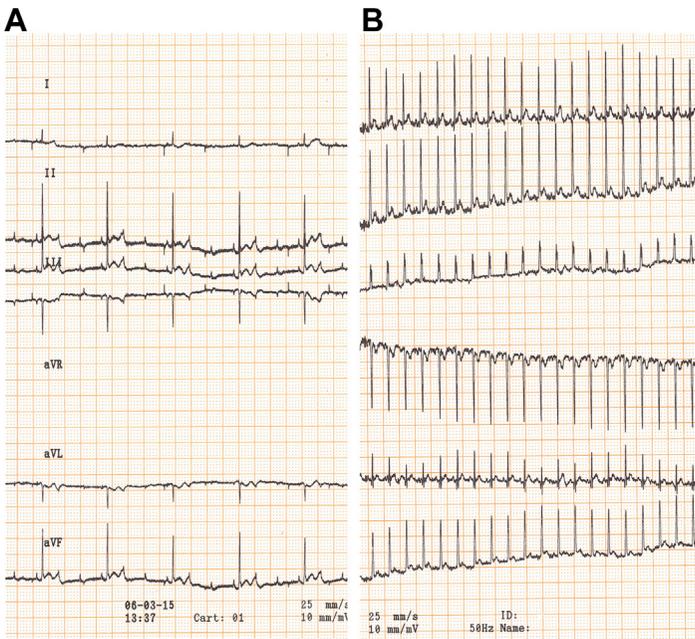


Fig. 7. An ECG of a ferret with a second-degree type II AV block (A). In type II blocks, the PR interval is constant, and there is a fixed relationship between the atrial and ventricular rate of, for example, 2:1, meaning 2 P waves to every QRS complex. Twenty minutes after administration of atropine (0.05 mg/kg IM), the block disappeared, and a fully normal ECG was seen (B).

3. Evaluate the duration and amplitude of each of the complexes and intervals in lead II. **Table 2** lists reference ranges for the different measurements.
4. Determine the mean electrical axis (MEA) through measuring net deflections in 2 leads (most often lead I and III; **Fig. 8**).

Blood Pressure Measurement

Because of the relative inaccessibility of peripheral arteries, direct arterial blood pressure measurement is not feasible in clinical practice for ferrets. Indirect systolic blood pressure measurements can be obtained using a Doppler and pressure cuff placed around the front limb, hind limb, or tail.¹⁴ Proper cuff size, that is, approximately 40% of the circumference of the extremity, is important, as too large cuff sizes can result in underestimation of actual blood pressure. A study on the accuracy and precision of indirect arterial blood pressure measurement using high-definition oscillometry showed that the method can be used in ferrets. With adequate sedation (ie, butorphanol and midazolam, 0.2 mg/kg each), reference ranges were established at 95 to 155, 69 to 109, and 51 to 87 mm Hg for systolic, mean, and diastolic arterial pressure.¹⁵

GENERAL MANAGEMENT OF CARDIAC DISEASE IN FERRETS

Medical management of cardiac disease in ferrets is similar to that of dogs and cats.^{1,3,4} In most instances, no specific pharmacokinetic or pharmacodynamic data are available for cardiac drugs in ferrets. Therefore, feline doses are often used as a starting point for therapy. **Table 3** provides an overview of drugs that can be indicated in ferrets with cardiovascular disease.⁴

Three mainstays in the treatment of acute congestive heart failure are as follows: (1) providing supplemental oxygen, for instance, in an incubator; (2) reducing the preload by giving diuretics (eg, furosemide, thiazide, spironolactone) or nitroglycerin (a venous dilator); and (3) reducing the afterload by giving angiotensin-converting enzyme (ACE) inhibitors, which induce vasodilatation and decrease water and salt retention (thereby

Table 2
Electrocardiographic reference values obtained in 20 awake ferrets placed in dorsoventral position

Parameter	Mean ± SD	Range
Heart frequency (bpm)	220	175–265
Heart axis (°)	88.5 ± 5.5	85–102
Measurements in lead II		
P duration (s)	0.019 ± 0.003	0.01–0.02
P amplitude (mV)	0.11 ± 0.04	0.09–0.2
PR interval (s)	0.049 ± 0.009	0.04–0.07
QRS duration (s)	0.026 ± 0.006	0.02–0.04
QRS amplitude (mV)	2.9 ± 1.2	1.4–4.4
QT interval (s)	0.14 ± 0.02	0.11–0.16
ST segment (mV)	0.03 ± 0.01	0.02–0.05
T duration (s)	0.084 ± 0.018	0.06–0.11
T amplitude (mV)	0.26 ± 0.08	0.15–0.4

(derived from Zandvliet, 2004).¹³

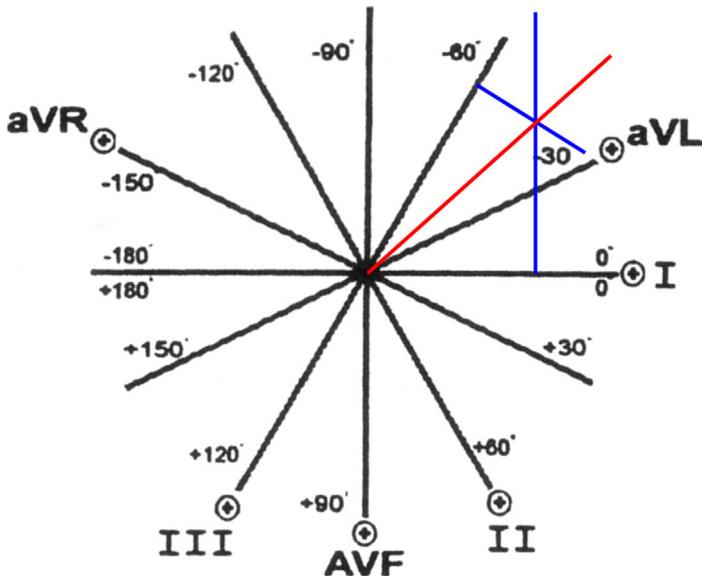


Fig. 8. To determine the mean electrical axis (MEA), the net deflections for the QRS complexes are measured in lead I and III and marked off from the zero point in the triaxial system. Next, perpendicular lines (blue) are drawn originating from the end points of the deflections until they intersect. A connecting arrow (red) is then drawn between the origin and the point of intersection, following which the MEA can be determined as the angle between the lead I axis (horizontal plane) and the connecting arrow. AVF, **augmented Vector Foot**; aVR, **augmented Vector Right**; aVL, **augmented Vector Left**.

also reducing the preload). In case of significant pleural effusion, thoracocentesis can be performed to alleviate dyspnea. In a stabilized animal with contractility dysfunction, pimobendan may be added to enhance inotropy.⁴

Beta-blockers (eg, atenolol) or calcium channel blockers (eg, diltiazem) can be used to reduce the heart rate and treat supraventricular and ventricular arrhythmias. In the case of ventricular tachycardias, IV lidocaine can be titrated to effect, whereas atropine may be indicated if bradycardia or bradyarrhythmia is present. However, as atropine only results in a short-term effect, long-acting parasympatholytic drugs (eg, propantheline) should be used for maintenance. Sympathomimetic drugs (metaproterenol, isoproterenol) have also been used in the medicinal therapy of third-degree heart block. However, if these are not effective, pacemaker implantation should be considered (Fig. 9).¹⁶

CARDIAC DISEASES

Congenital Heart Disease

In ferrets, the following congenital heart defects have been reported: (1) atrial and ventricular septal defects ($n = 1$ for both)^{17,18}; (2) an AV canal defect ($n = 1$)¹⁹; (3) tetralogy of Fallot ($n = 3$)²⁰⁻²²; and (4) patent ductus arteriosus (PDA).²³

Clinical signs

Congenital heart disease has been diagnosed in ferrets up to 6 years. Dependent on the size and type of defect, animals may be symptomless, or die before or shortly after birth. Growth retardation can be seen, and animals may develop pulmonary edema,

Table 3
Drugs to be used in the treatment of cardiovascular disease in ferrets⁴

Drug	Action	Dosage
Amlodipine	Calcium antagonist; afterload reduction	0.2–0.4 mg/kg po q12h
Atenolol	Beta-blocker for treatment of HCM	3.125–6.25 mg/kg po q24h
Atropine	Parasympatholytic drug for treatment of bradycardia	0.02–0.05 mg/kg SC/IM
Benazepril	ACE inhibitor; vasodilator	0.25–0.5 mg/kg po q24h
Captopril	ACE inhibitor; vasodilator	1/8 of 12.5 mg tablet/animal po q48h
Digoxin	Positive inotropic drug for treatment of DCM	0.005–0.01 mg/kg po q12–24h
Diltiazem	Calcium channel blocker for treatment of HCM, AF, or SVT	1.5–7.5 mg/kg po q12h
Dobutamine	Sympathomimetic drug used in treatment of heart failure and cardiogenic shock	5–10 µg/kg/min IV (canine dose)
Enalapril	ACE inhibitor; vasodilator	0.25–0.5 mg/kg po q24–48h
Furosemide	Loop diuretic for treatment of congestion	1–4 mg/kg po/SC/IM/IV q8–12h
Hydrochlorothiazide	Diuretic for treatment of congestion; may be combined with spironolactone	1 mg/kg po q12–24h (cat dose)
Isoproterenol	Sympathomimetic drug for treatment of 3rd-degree AV block	40–50 µg/kg po/SC/IM q12h
Ivermectin	Broad-spectrum antiparasitic avermectin for treatment of heartworm	0.02 mg/kg po/SC (preventative) or 50 µg/kg SC q30d (treatment)
Melarsomine	Arsenical; adulticide used to treat heartworm disease	2.5 mg/kg IM at day 1, 30, 31
Metaproterenol	Sympathomimetic drug for treatment of 3 rd -degree AV block	0.25–1 mg/kg po q12h
Milbemycin oxime	Broad-spectrum antiparasitic milbemycin; prevention of heartworm disease	1.15–2.33 mg/kg po q30d
Moxidectin	Broad-spectrum antiparasitic avermectin; used to treat heartworm (adulticide)	0.1 mL SC (single dose); use every 6 mo as preventative treatment
Nitroglycerin	Vasodilator	1/16–1/8 in per animal of a 2% ointment q12–24h, applied to shaved inner thigh or pinna
Pimobendan	Phosphodiesterase inhibitor; increase cardiac contractility in patients with DCM	0.5–1.25 mg/kg po q12h
Propranolol	Beta-blocker for treatment of HCM	0.2–1 mg/kg po/SC q8–12h

(continued on next page)

Table 3 (continued)		
Drug	Action	Dosage
Propranolol	Long-acting parasympatholytic for treatment of sinus bradyarrhythmia	0.25–0.5 mg/kg po 8–12 hours (canine dose)
Selamectin	Broad-spectrum antiparasitic avermectin; used as preventive treatment for heartworm	18 mg/kg topically
Spirolactone	Diuretic for treatment of congestion	1–2 mg/kg po q12h
Theophylline	Methylxanthine drug, which serves as a bronchodilator (relaxation of bronchial smooth muscles) and also has positive inotropic and chronotropic effects	4.25 mg/kg po q8–12h

pleural effusion, hepatomegaly, and/or ascites as a result of congestive heart failure, which may lead to dyspnea, tachypnea, cough, muscle wasting, and/or distended abdomen. On physical examination, a (holodiastolic, holosystolic, or continuous) cardiac murmur will often be audible. In addition, a tachycardia, faint pulse, cyanotic or pale mucous membranes, and/or prolonged CRT can be present.

Diagnosis

Echocardiography is the preferred technique to be used for diagnosing congenital heart abnormalities. Color Doppler ultrasonography may be useful to detect left-to-right or right-to-left shunting, or turbulent blood flow owing to stenosis or valvular insufficiencies (Fig. 10). Secondary cardiac changes (eg, atrial dilatation, concentric or eccentric ventricular hypertrophy) may also be noted.

Radiographs can reveal an enlarged cardiac silhouette and signs of congestive heart failure (eg, pulmonary edema, pleural effusion ascites).

Treatment

Mild congenital heart defects in asymptomatic ferrets may not require any treatment. However, regular monitoring is recommended so that developing congestive heart



Fig. 9. A 6-year-old neutered female ferret with a recently placed transvenous pacemaker for management of a third-degree heart block.

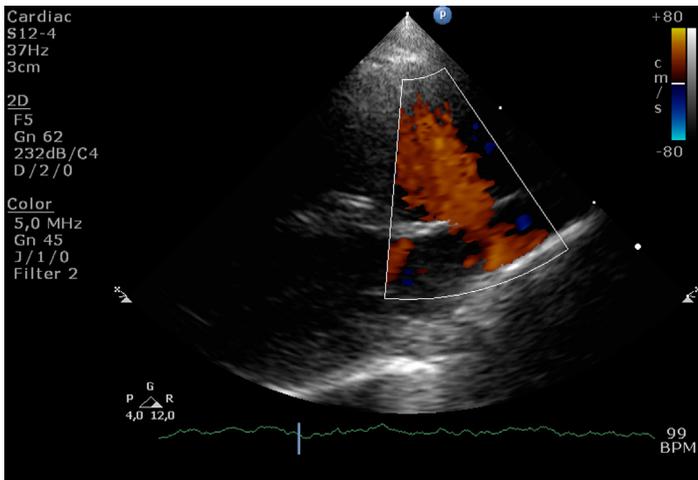


Fig. 10. Color-flow Doppler demonstrates a direct blood flow between both atria in a 2-year-old, male castrated ferret with an atrial septal defect. (Previously printed in *Journal of Exotic Pet Medicine* 2013 22 (1): 70 to 75.)

failure can be caught early and treated promptly. Treatment is indicated in animals with congestive heart failure (eg, furosemide, enalapril, pimobendan, digoxin, atenolol). Surgical intervention, which is performed in dogs with, for example, PDA, has not been described in ferrets.

Acquired Heart Disease

Dilated cardiomyopathy (DCM) and acquired valvular disease (AVD; endocardiosis or myxomatous valvular degeneration) are the most common acquired heart diseases to be encountered in ferrets.^{3,4} Other, less frequently reported cardiac conditions include infectious diseases (such as fungal or bacterial myocarditis, endocarditis, or pericarditis, toxoplasmosis, heartworm disease or dirofilariasis, and Aleutian disease), neoplasia (eg, lymphoma, lymphosarcoma), hypertrophic cardiomyopathy (HCM), and pericardial effusion.^{3,4,24}

Dilated Cardiomyopathy

(DCM is most common in middle-aged to older ferrets, with no sex predilection reported.¹⁻⁴ DCM is characterized by an increased diastolic dimension and systolic dysfunction of the left and/or right ventricles. Histologically, DCM is characterized by multifocal myocyte degeneration and necrosis, myofiber loss, and replacement fibrosis. Occasionally, inflammatory infiltrates may be present.²⁵ The exact cause is unknown, although nonconfirmed associations with taurine or carnitine deficiencies have been made. Preexisting endocrine disease, intoxications, or infectious disease (eg, viruses, cryptococcus),²⁶ as well as a genetic origin may also play a role in the development of the disease.⁴

Clinical signs

Clinical signs may develop from completely asymptomatic to lethargy, weakness, anorexia, weight loss, exercise intolerance, and respiratory distress (tachypnea, dyspnea, cough). Physical examination may reveal a weak pulse, pulse deficit, tachycardia (>250 bpm), (systolic) heart murmur, gallop rhythm/arrhythmia, hypothermia,

pallor, cyanosis, increased respiratory effort, muffled heart and lung sounds, moist rales or crackles, increased respiratory sounds, prolonged CRT, posterior paresis, hepato(spleno)megaly, or ascites.^{1-4,27}

Diagnosis

Characteristic echocardiographic findings include thin ventricular walls, dilatation of the left ventricle with increase in end-systolic and end-diastolic dimensions, enlargement of the left atrium, and reduced fractional shortening (Fig. 11). Outflow tract velocities of the left ventricle can be normal or reduced. Dilatation of the right ventricle and atrium indicates involvement of the right side. In advanced stages, mitral valve and tricuspid insufficiency and regurgitation can be identified with Doppler ultrasound. Similarly, signs of pleural effusion, liver congestion, and/or ascites can be observed.^{1,3,4}

Radiographs are useful to identify pleural effusion or pulmonary edema, or to rule out mediastinal lymphoma. If the abdomen is included in the radiograph, the presence of hepatomegaly or splenomegaly, or ascites can be evaluated.

ECG can be normal or reveal atrial and ventricular premature contractions, atrial or ventricular tachycardia, atrial fibrillation, and first- or second-degree heart block. Signs of left atrial or ventricular enlargement (eg, broadened P wave, reduced voltage, and/or widened QRS complexes) can also be present.^{3,4}

Routine blood tests and urinalysis will generally not reveal abnormalities unless severe heart failure is present, resulting in prerenal azotemia, hyponatremia and increased ALT concentrations, or concurrent disease. B-type natriuretic peptide and N-terminal pro b-type natriuretic peptide levels are currently of limited clinical use.

Treatment/management

Initial treatment includes provision of oxygen, diuretics (eg, furosemide, thiazide, spironolactone), and thoracocentesis (if pleural effusion is present). Monitoring of the

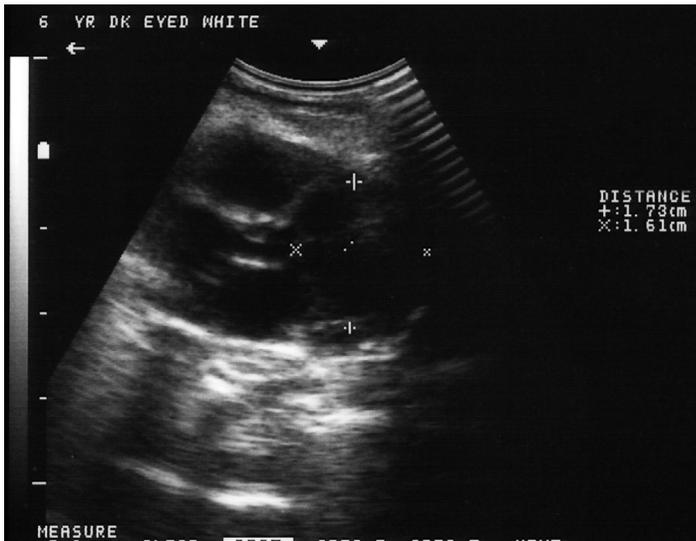


Fig. 11. Cardiac ultrasound of a 6-year-old ferret with DCM. The inner diameter of the left ventricle was 1.7×1.6 cm (reference <1.3 cm in ferrets). In addition to a dilated ventricle, a decreased wall thickness and decreased FS may also be observed. (Photo courtesy of Cathy Johnson-Delaney. Previously printed in Disorders of the cardiovascular system. Ferret Medicine and Surgery.)

respiratory rate and effort, and auscultating lung sounds are helpful to evaluate treatment response. Stress should be avoided at all costs, as this may lead to death.^{3,4}

Following stabilization, the diuretic dose is adjusted, if needed, whereas ACE inhibitors, pimobendan and/or digoxin (in case of tachycardia), can be added to the treatment protocol. The dose of diuretics should be reduced to the lowest dose that prevents reaccumulation of pleural effusion and pulmonary edema, as overzealous administration of diuretics may result in dehydration and hypokalemia. ACE inhibitors (eg, enalapril) are recommended for long-term therapy to help reduce preload and afterload, improve cardiac output, and reduce congestion. Careful monitoring is recommended, as ferrets are suggested to be sensitive to the hypotensive effects of ACE inhibitors, thereby quickly becoming weak and lethargic. Pimobendan and digoxin are indicated to increase ventricular contractility. For severe systolic dysfunction, a combination of both drugs may be beneficial. Pimobendan acts as a positive inotrope and vasodilator, thereby helping to reduce preload and afterload. Digoxin is indicated (with or without propranolol) in ferrets with atrial fibrillation to slow down the heart rate to 180 to 250 bpm in resting state. The narrow therapeutic window warrants careful monitoring of serum concentrations (therapeutic range: 1–2 ng/mL 6–12 hours following oral administration) and clinical signs of toxicity (eg, anorexia, nausea, vomiting, and lethargy), especially in ferrets with renal insufficiency. Periodic monitoring is recommended, which should include a physical examination, echocardiography, electrocardiography, and measurement of urea or blood urea nitrogen, and electrolytes.^{3,4}

Prognosis

If diagnosed in an early stage, prognosis appears fair, with ferrets often responding well to therapy and living a good quality of life for several months, up to 2 years. If disease is more advanced, prognosis is considered more guarded. Sudden death may occur because of life-threatening arrhythmias.

Heartworm Disease (*Dirofilaria*)

Heartworm disease, caused by infection with *D immitis*, is an uncommon disease in ferrets.^{28–30} Mosquitoes serve as a vector and intermediate host for the parasite. The susceptibility and life cycle of *D immitis* are similar to those in dogs.^{31–34} Ferrets are considered aberrant hosts, with those that live (outdoors) in or originate from heartworm endemic areas (ie, along the Atlantic and Gulf coast, in tropical and semitropical areas) being most at risk to develop disease.

Worms can reside in the right ventricle, cranial vena cava, or main pulmonary artery and cause villous endarteritis. Even a single worm can lead to severe heart disease, and as few as 2 adult heartworms have resulted in fatal right-sided heart failure owing to mechanical obstruction of the blood flow.³

Clinical presentation

Clinical signs are similar to those observed in cats and may range from asymptomatic individuals to sudden death, resulting from pulmonary artery obstruction. Other clinical signs include anorexia, lethargy, weakness, depression, dyspnea, tachypnea, cyanosis, coughing, pale mucous membranes, abdominal distension, and rarely, melena.^{3,28–31} Physical examination may reveal labored breathing, crackles, and moist rales in the case of pulmonary edema, or shallow breathing, decreased chest compliance, and muffled heart and lung sounds in the case of pleural effusion. Ascites, hepatomegaly, and splenomegaly may be present in the case of right-sided heart failure. Upon heart auscultation, a tachycardia and/or heart murmur can sometimes be heard. Occasionally, arrhythmias (most commonly atrial fibrillation) can be identified. Caval

syndrome, frequently leading to hemoglobinemia, hemoglobinuria, and hemolytic anemia, as well as renal and hepatic dysfunction, has been reported in ferrets and may be life threatening. Aberrant larval migration, with associated central nervous system signs, has also been documented in one ferret with a *D immitis* infection.³¹

Diagnosis

Because of the rapid progression of the disease, heartworm should be diagnosed as early as possible. Echocardiography is most useful in the diagnosis, as the adult worms may be visualized in the pulmonary artery, right ventricle, and/or right atrium as parallel, linear echodensities.³⁵ Right atrial and ventricular dilation can be noted. Doppler echocardiography may confirm the presence of pulmonary hypertension. Thoracic radiographs can reveal pleural effusion, ascites, and cardiomegaly.³⁴ Enlargement of the caudal vena cava, right atrium, and right ventricle are often seen, whereas peripheral pulmonary arterial changes are rare in ferrets.

Serologic tests that identify adult *D immitis* antigen are the first choice in diagnosing infection, although little is known regarding its sensitivity and specificity in ferrets. Because the test will only detect antigen that is shed by the adult female heartworms, and multiple worms are needed to produce enough antigen, false negative results may occur with low worm burdens (<5 worms). A modified Knott test can be performed to detect circulating microfilaria. However, peripheral microfilaremia only seems present in half of the affected animals, thereby limiting the usefulness of this test.^{3,4}

Treatment

Ivermectin (0.05–0.1 mg/kg every 30 days SC) is the preferred drug of treatment and needs to be administered until resolution of the clinical signs and microfilaremia. Other protocols include the use of adulticides, such as melarsomine (Immiticide, Rhone Merieux; 2.5 mg/kg IM followed by 2 injections 24 hours apart 1 month later) and thiactarsemide (0.22 mL/kg every 12 hours IV for 2 days). Moxidectin (0.1 mL SC) has anecdotally been suggested as an effective and safe adulticide.³⁶ If microfilaremia is present, a microfilaricide therapy should be initiated 4 to 6 weeks following adulticide therapy.^{3,4} Microfilaricides that have been used include dithiazanine iodide (6–20 mg/kg by mouth) or milbemycin oxime (1.15–2.33 mg/kg by mouth every 30 days), although therapeutic efficacy of the latter has not been clearly documented. Transvenous heartworm extraction is nowadays also a viable option,³² especially because adulticide therapy has fallen out of favor because of anecdotal adverse reactions, including sudden death and myositis at the injection site.

Complications may arise from worm emboli. As a result, prednisone (0.5–1 mg/kg every 12–24 hours by mouth) is often initiated concurrently with the adulticide treatment and continued for at least 4 months. Strict cage rest and restriction of exercise are advised for a minimum of 4 to 6 weeks following adulticide therapy.

Symptomatic ferrets may require stabilization and treatment for heart failure (including oxygen, furosemide, enalapril, and theophylline) before initiating adulticide treatment. Thoracocentesis is indicated in ferrets with pleural effusion.

A follow-up enzyme-linked immunosorbent assay for heartworm antigen can be performed approximately 3 months after initiating therapy. Testing is then repeated on a monthly basis until results are negative (usually 4 months following successful adulticide therapy). Further tests (eg, radiographs, echocardiography) may be warranted if test results remain positive.^{3,4}

Prevention

Control is best achieved through monthly administration of a heartworm preventative. This includes the administration of ivermectin (0.05 mg/kg every 30 days by mouth or

SC), milbemycin oxime (1.15–2.33 mg/kg every 30 days by mouth), selamectin (18 mg/kg topically), or moxidectin (0.1 mL [single dose] SC, repeat every 6 months). Prevention should start 1 month before and continue until 1 month after the heartworm season. Housing ferrets indoors, particularly during the mosquito season, may also help to minimize exposure.^{3,4}

Endocarditis

Endocarditis has rarely been documented in ferrets.^{37,38} It is characterized by an inflammation of the endocardial tissues, that is, the valves (endocarditis valvularis), the wall (endocarditis parietalis), or chordae tendineae (endocarditis chordalis), and can be bacterial or nonbacterial in origin.

Clinical presentation

Clinical signs may include lethargy, anorexia, weight loss, lameness, and pyrexia. Hemorrhage may occur if the animal develops diffuse intravascular coagulation. A cardiac murmur may be heard upon auscultation.

Diagnosis

A bacterial endocarditis is usually diagnosed based on 2 or more positive blood cultures in addition to echocardiographic evidence of vegetations or valve destruction, or the documented recent onset of a (regurgitant) cardiac murmur. However, negative cultures do not rule out the possibility of bacterial endocarditis, and structural abnormalities and vegetations visualized during echocardiography will be difficult to differentiate from endocardiosis.

Nonbacterial endocarditis may present on echocardiography as an irregular thickening of the valve leaflets, with normal chamber dimensions and normal systolic function.³⁷

Treatment

Bacterial endocarditis requires prolonged antibiotic treatment (ie, over the course of at least 4 weeks), using either a broad-spectrum antibiotic or one that is appropriate based on culture and sensitivity results. In addition, symptomatic treatment, aimed at alleviating the clinical signs, is initiated. However, survival seems poor, with none of the reported ferrets surviving for more than 3 days.

Hypertrophic Cardiomyopathy

HCM is a rare condition in (younger) ferrets.^{1,3,4} The cause is currently unknown. HCM is characterized by concentric hypertrophy (ie, increased wall thickness) of the left ventricular wall and interventricular septum. Histologically, HCM is characterized by hyperplasia of the individual myofibers, primarily of the left ventricle.

Clinical presentation

Clinical presentation may range from an asymptomatic ferret to sudden death (especially during anesthesia) without preemptive signs.² Clinical signs are linked either to the reduced cardiac output resulting from the impaired ventricular filling (eg, weakness manifesting by paresis posterior, ataxia) or to the increased filling pressure in the left ventricle, which results in pulmonary congestion (left-sided heart failure). A physical examination may reveal a weak or irregular pulse, tachycardia, (S3 or S4) gallop rhythm, arrhythmias, and/or systolic heart murmur. In the case of pulmonary congestion, increased respiratory sounds, moist rales, and/or crackles can be heard.^{3,4}

Diagnosis

Ultrasound may reveal (generalized or local) gross thickening of the interventricular septum and/or left ventricular free wall and decreased left ventricular dimensions. Fractional shortening may be normal or increased. Left atrial enlargement or systolic anterior mitral valve motion (associated with interventricular septum hypertrophy) can also be seen. Doppler echocardiographic evaluation may reveal turbulence in the left ventricular outflow tract secondary to dynamic obstruction and mitral regurgitation.^{3,4}

Radiographs may reveal a normal to increased cardiac silhouette or, in the case of (left-sided) heart failure, signs of pulmonary edema or pleural effusion. Electrocardiography may reveal sinus tachycardia (>280 bpm) and, occasionally, atrial or ventricular premature contractions. Widened QRS complexes of increased amplitude, and signs of atrial enlargement (ie, broadened P wave) may also be noted.

Treatment

Treatment is aimed at eliminating heart failure (if present) and, following stabilization, improving the diastolic filling of the ventricles. Beta-blockers, for example, propranolol (0.2–1.0 mg/kg every 8–12 hours by mouth) or atenolol (3.1–6.2 mg every 24 hours by mouth), are commonly recommended to reduce heart rate and correct atrial and ventricular arrhythmias. In addition, calcium channel blockers (eg, diltiazem, 3.7–7.5 mg every 12 hours by mouth) can be administered to reduce heart rate, improve diastolic relaxation and ventricular filling, and induce vasodilatation, which helps to reduce preload and afterload and increase myocardial perfusion (through vasodilatation of the coronary arteries). Combined, the drugs help to reduce myocardial oxygen consumption and increase cardiac output, but careful monitoring is warranted, as overdosing may lead to significant bradycardia, hypotension, lethargy, and/or inappetence.

Treatment with diuretics and ACE inhibitors may be considered if heart failure is present. Positive inotropic drugs should be avoided. Aspirin or heparin therapy is not considered necessary because of the rare incidence of arterial thromboembolism in ferrets.^{3,4}

Myocarditis

Myocarditis is a focal or diffuse inflammation of the myocardium with myocyte degeneration and/or necrosis, which results in reduced myocardial function, arrhythmias, and, in the end stages, replacement fibrosis. Myocarditis can occur as part of a systemic vasculitis, autoimmune disease, intoxication (eg, doxorubicin cardiotoxicosis), traumatic injury (eg, cardiac puncture or ischemic events), or parasitic, bacterial, fungal, or viral infection. Myocarditis may also occur secondary to an endocarditis or inflammatory process elsewhere in the body.^{3,4}

Myocarditis is rarely diagnosed in ferrets. In those cases that have been described, a toxoplasma-like organism, Aleutian disease (a parvoviral infection), bacterial and fungal infections in the myocardium, have played a role.^{39,40}

Clinical presentation

The clinical signs generally result from systolic dysfunction or pathologic arrhythmias that can occur, leading to classic signs of congestive left or right heart failure (eg, dyspnea, tachypnea, ascites), or sudden death owing to onset of ventricular tachycardia or ventricular fibrillation. Other signs include lethargy, anorexia, and fever. A heart murmur, resulting from mitral or tricuspid valve regurgitation, may be audible on auscultation, as well as an irregular heart rhythm.^{3,4}

Diagnosis

The gold standard is histologic evaluation of the myocardium. However, obtaining cardiac biopsies is difficult, thereby hindering antemortem diagnosis. Diagnosis therefore usually is presumptive and based on exclusion of other causes. ECG may reveal atrial fibrillation or ventricular and/or atrial premature complexes, whereas chamber dilation and poor ventricular contractility with essentially normal valves may be noted on echocardiography. Leukocytosis, neutrophilia, and hyperfibrinogenemia can be noted in the hematologic and biochemical profile. Cardiac isoenzymes (creatinine kinase, lactate dehydrogenase, and troponin) are often increased. Serum cardiac troponin T (cTnT) and I (cTnI) are considered sensitive and specific indicators of myocardial damage (eg, owing to ischemia or inflammation) in humans and other animals and may thus be of use in ferrets. However, reference ranges (ie, 0.05–0.10 ng/mL) are below the detection limit of commercially available assays.³ Combined with a lack of clinical trials or controlled studies, this limits the current clinical use of cTnT and cTnI in ferrets.

Treatment

Treatment is aimed at eliminating the primary cause and alleviating symptoms related to congestive heart failure and arrhythmias. Pimobendan or digoxin can improve the cardiac contractility, whereas furosemide helps to control signs of pulmonary edema, pleural effusion, or ascites. Corticosteroids may be considered in the absence of an infectious cause.

Neoplasia

Neoplasia involving the myocardium or pericardium is rare in ferrets, with only one case of an atrial tumor being reported in the literature.² In addition, the authors have diagnosed a ventricular sarcoma in a 5-year-old male ferret. This ferret presented with dyspnea of sudden onset as a result of pleural effusion. Upon auscultation, a gallop rhythm could be heard. As the ferret died shortly after presentation in the clinic, the diagnosis was only made at postmortem examination.⁴

Restrictive Cardiomyopathy

Restrictive cardiomyopathy, which is defined as a clinically normal-appearing left ventricle combined with left atrial enlargement, is rare in ferrets.⁷ As a result of scar formation following inflammation, the heart muscle is stiffened and can no longer expand, preventing normal filling of the ventricles (ie, diastolic dysfunction).

Diagnosis

Definite diagnosis requires documentation of diastolic dysfunction during ultrasound (eg, using tissue Doppler imaging) or histologic evaluation of cardiac tissue.

Treatment

Treatment follows similar guidelines as those described for HCM. In cats, prognosis of restrictive cardiomyopathy appears guarded to poor, with animals rarely surviving for longer periods of time and often responding poorly to therapy. Prognosis in ferrets is likely similar.

Valvular Disease (Acquired) or Endocardiosis

AVD or endocardiosis is recognized with increasing frequency in middle-aged to older ferrets. It is characterized by degenerative changes and depositions of proteoglycans and glycosaminoglycans in the subendocardial valve leaflets and chordae tendineae.^{3,4,7} The aortic and mitral valves appear most commonly affected. Gross lesions

include opaque nodular thickening and shortening at the free edge and base of the valve leaflets. Secondary dilatation of the left atrium and ventricle may occur.^{3,4}

Clinical presentation

Mitral valve regurgitation often results in a systolic murmur, which is best heard over the left apical region, whereas tricuspid valve regurgitation is best auscultated in the right parasternal location.² Aortic insufficiency, presenting as a diastolic murmur, is rarely heard on auscultation. Additional signs can be observed if congestive heart failure and may include a weak pulse, abdominal distension resulting from hepatosplenomegaly and/or ascites, dyspnea, tachypnea, coughing, increased respiratory sounds, moist rales or crackles, or muffled heart and lung sounds.^{3,4}

Diagnosis

Echocardiographic findings may include cardiomegaly, atrial and/or (mild) ventricular dilatation, thickening of the valves, and a normal to increased fractional shortening with normal ventricular contractility and wall thickness. Valvular regurgitation can be identified and quantified using color-flow and/or pulse-wave Doppler. Note that small regurgitant jets of blood can occur in clinically healthy ferrets, which should not be mistaken for cardiac pathologic condition.^{3,4}

Thoracic radiographs can be useful to evaluate cardiac size and establish whether signs of congestive heart failure (pulmonary edema, pleural effusion, ascites) are present. Electrocardiography is often unremarkable but may include signs of atrial enlargement (ie, broadened P wave) or atrial arrhythmias.^{3,4}

Treatment

Therapy is not recommended as long as ferrets are asymptomatic. If signs of congestive heart failure are present, treatment may be initiated with furosemide and ACE inhibitors (eg, enalapril) to alleviate the neurohormonal activation of the Renin-Angiotensin-Aldosterone System (RAAS) that occurs with advanced cardiac disease and congestive heart failure. In the case of impaired systolic function and/or supraventricular arrhythmias, positive inotropic drugs, such as pimobendan and digoxin, may be given once the ferret has stabilized.^{3,4}

Pericardial Effusion and Pericarditis

Pericardial effusion is characterized by the presence of an abnormal amount of fluid between the heart and the pericardium and may result from inflammation of the pericardium (ie, pericarditis). Pericardial effusion can occur as a primary condition or secondary to other medical conditions (eg, viral or bacterial infections, neoplasia, uremia, autoimmune disease, trauma, coagulopathies, hypoalbuminemia, cardiomyopathy, and right-sided heart failure). Primary pericardial effusion without concurrent disease has thus far not been reported in ferrets.⁴

Clinical signs

Dependent on the amount of fluid present in the pericardial sac, clinical signs may be totally absent or result in significant disease owing to impaired filling of the ventricles (ie, cardiac or pericardial tamponade). If the pericardial effusion builds up slowly, the left ventricular function often remains intact, and only signs associated with right-sided heart failure (ie, hepatomegaly, ascites, pleural effusion with concurrent dyspnea, tachypnea and cough, and exercise intolerance) will develop. However, a rapidly developing pericardial effusion may compromise both left and right ventricular outflow, thereby resulting in severe shock, syncope, and potentially death. Animals with minor to moderate pericardial effusion can remain asymptomatic, with pericardial

effusion noted as a coincidental finding during echocardiography. Physical examination will often reveal a weak pulse and so-called pulsus paradoxus (a drop in arterial blood pressure concurrent with inspiration), as well as muffled cardiac sounds and tachycardia.⁴

Diagnosis

Echocardiography is used to identify the presence of excess fluid surrounding the heart, whereas ECG can reveal low-voltage QRS complexes and pulsus alternans (ie, changing amplitude of the QRS complexes).

Pericardiocentesis can help to identify the cause of the pericardial effusion. The collected fluid may be submitted for cytologic analysis, biochemical analysis, and/or (bacterial) culture.⁴

Treatment

Small pericardial effusions in asymptomatic animals often require no special treatment. For pericardial effusion owing to pericarditis or secondary to other diseases, treatment should be aimed at the initiating cause. Severe pericardial effusions with cardiac impairment warrant drainage by pericardiocentesis. In the case of recurrence and/or idiopathic pericardial effusion, pericardiectomy may be considered (although this has not yet been described in ferrets).⁴

Cardiac Arrhythmias and Conduction Disturbances

Cardiac arrhythmias and conduction abnormalities may occur as a result of changes in the electrical conduction system of the heart and can be physiologic or pathologic in origin. Sinus arrhythmia is the most common physiologic arrhythmia noted and may be caused by respiration or an increased vagal tone. Sinus tachycardia and second-degree AV block have also been reported to occur physiologically in healthy ferrets.^{4,7}

Pathologic arrhythmias can result following stress, pain, hyperthermia, hypoxia, shock, electrolyte or metabolic disturbances (eg, hypercalcemia, hypokalemia, or hyperkalemia), infections (eg, sepsis), intoxications (eg, digoxin), anesthesia, endocrine disease (eg, hyperthyroidism), anemia, and cardiac abnormalities (eg, DCM, myocarditis).⁴

Clinical presentation

Cardiac arrhythmias and conduction abnormalities can largely remain undetected until they are discovered as a coincidental finding during a routine auscultation or electrocardiography. Dependent on the type of arrhythmia or conduction disturbance that is present, irregular pulse waves or pulse deficits may be palpated. (Life-threatening) bradycardia (<120 bpm), with subsequent lethargy, weakness, exercise intolerance, and syncope, may result from second- and third-degree AV blocks.^{16,41} Congestive heart failure and hypoperfusion may develop once the heart rate consistently drops to less than 80 bpm. In animals with severe tachycardia (>300 bpm), similar signs may be noted, with ventricular tachycardias quickly resulting in death if not promptly treated.⁴ Because of impaired cardiac filling and output, the pulse in these animals will often be weak.

Diagnosis

Electrocardiography is required to identify the type of arrhythmia or conduction disturbance and establish a definite diagnosis. Bradycardia warrants the use of an atropine response test to determine vagal involvement.⁴ Other diagnostic tests (eg, echocardiography, radiography, hematology, and biochemistry) may be useful to rule out underlying disease.

Treatment

In the case of tachycardia or tachyarrhythmia, antiarrhythmic drugs, such as lidocaine, digoxin, or beta-blockers (eg, propranolol, atenolol), are indicated to lower the heart rate. Ferrets with clinical signs resulting from high-grade second-degree and third-degree AV block may benefit from anticholinergics (eg, propantheline), beta-adrenergics (eg, terbutaline, isoproterenol), and phosphodiesterase inhibitors (eg, aminophylline, theophylline), particularly if heart rate increased following atropine administration.⁴ In animals with little response to aforementioned medications, pace-makers may be implanted.¹⁶ Treatment furthermore comprises alleviation of the clinical signs as well as eliminating the underlying cause.

Prognosis

Most electrocardiographic abnormalities that have been identified in ferrets are discovered by coincidence and will not affect the animal in any way. Profound bradycardia (<80 bpm), as can be seen with high-degree second- or third-degree AV block, carries a poor prognosis if not treated promptly.

SUMMARY

While most common in middle-aged to older ferrets, cardiac disease should be considered in the differential diagnosis of any ferret displaying signs of weakness, lethargy or dyspnea. Commonly, heart failure results from dilated cardiomyopathy, but hypertrophic cardiomyopathy, valvular disease and other cardiac conditions may certainly also occur. Hence, geriatric patients may benefit from routine check-ups which include cardiac monitoring. If suspecting cardiac disease, diagnostic modalities such as ultrasound, radiographs and ECG may help establish a definitive diagnosis, which can serve as an important starting point for therapeutic intervention.

DISCLOSURE

The authors have nothing to disclose.

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