

THE FELINE CARDIOMYOPATHIES

3. Cardiomyopathies other than HCM



Practical relevance: Although feline hypertrophic cardiomyopathy (HCM) occurs more commonly, dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction (LVNC) and cardiomyopathy – nonspecific phenotype (NCM; formerly unclassified cardiomyopathy) are all recognized in domestic cats.

Patient group: Any adult domestic cat, of either sex and of any breed, can be affected.

Diagnostics: The non-HCM cardiomyopathies are rarely suspected in subclinically affected cats, so most are first identified when a cat presents with signs of heart failure or systemic thromboembolic disease. The definitive clinical confirmatory test for these other feline cardiomyopathies is echocardiography.

Key findings: 'Cardiomyopathy – nonspecific phenotype' is a catch-all term that groups hearts with myocardial changes that either do not meet the criteria for any one type of cardiomyopathy (HCM, RCM, DCM, ARVC, LVNC) or meet the echocardiographic criteria for more than one type. RCM is characterized by diastolic dysfunction due to fibrosis that results in a restrictive transmitral flow pattern on Doppler echocardiography and usually marked left or biatrial enlargement. DCM is characterized by decreased myocardial contractility and is rare in cats. When it occurs, it is seldom due to taurine deficiency. However, since taurine-deficient DCM is usually reversible, a diet history should be obtained, whole blood and plasma taurine levels should be measured and taurine should be supplemented in the diet if the diet is not commercially manufactured. ARVC should be suspected in adult cats with severe right heart enlargement and right heart failure (ascites and/or pleural effusion), especially if arrhythmia is present. Feline LVNC is rare; its significance continues to be explored. Treatment of the consequences of these cardiomyopathies (management of heart failure, thromboprophylaxis, treatment of systemic arterial thromboembolism) is the same as for HCM.

Conclusions: While these other cardiomyopathies are less prevalent than HCM in cats, their clinical and radiographic presentation is often indistinguishable from HCM. Echocardiography is usually the only ante-mortem method to determine which type of cardiomyopathy is present. However, since treatment and prognosis are often similar for the feline cardiomyopathies, distinguishing among the cardiomyopathies is often not essential for determining appropriate therapy.

Areas of uncertainty: The feline cardiomyopathies do not always fit into one distinct category. Interrelationships among cardiomyopathies in cats may exist and understanding these relationships in the future might provide critical insights regarding treatment and prognosis.

Keywords: Cardiomyopathies; myocardial diseases; restrictive cardiomyopathy; dilated cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy; left ventricular noncompaction; echocardiography

Dilated cardiomyopathy

The term dilated cardiomyopathy (DCM) is often defined as left ventricular (LV) dilation and depressed myocardial performance in the absence of systemic hypertension and valvular, congenital or ischemic heart disease.¹ While this definition was developed for humans, in cats DCM is expressed as an inherent myocardial disease that results in a decrease in contractility (myocardial failure) and conse-

quent ventricular eccentric hypertrophy. These inherent myocardial diseases can cause myocyte death and/or myocyte weakness. The defining feature is a decrease in global myocardial contractility that results in an increase in the LV end-systolic internal diameter (LVIDs) and volume of the affected ventricle (the weak ventricular myocardium cannot squeeze down as far as normal against the normal intraventricular systolic



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1. General concepts

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The material presented in this series of articles is based on an extensive literature review, and the experience of the authors. A collection of audio (auscultation) and video (physical examination, echocardiogram) material is appended online.

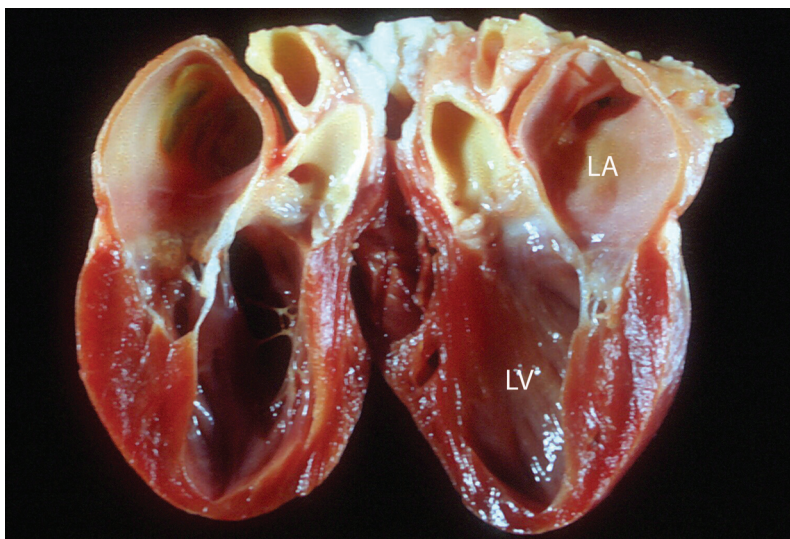
ABBREVIATIONS

- ❖ 2D = two-dimensional
- ❖ ARVC = arrhythmogenic right ventricular cardiomyopathy
- ❖ ATE = arterial thromboembolism
- ❖ cTn I = cardiac troponin I
- ❖ DCM = dilated cardiomyopathy
- ❖ ECG = electrocardiography or electrocardiographic
- ❖ HCM = hypertrophic cardiomyopathy
- ❖ IGF-1 = insulin-like growth factor 1
- ❖ LA = left atrium or left atrial
- ❖ LV = left ventricle or left ventricular
- ❖ LVIDd = left ventricular internal diameter in diastole
- ❖ LVIDs = left ventricular internal diameter in systole
- ❖ LVNC = left ventricular noncompaction
- ❖ MOGE(S) = morphofunctional phenotype, organ involvement, genetic inheritance pattern, etiology, functional status
- ❖ NCM = cardiomyopathy – nonspecific phenotype
- ❖ NT-proBNP = amino terminal pro-B-type natriuretic peptide
- ❖ PE = pulmonary edema
- ❖ PLE = pleural effusion
- ❖ RA = right atrium, right atrial
- ❖ RCM = restrictive cardiomyopathy
- ❖ RR = respiratory rate
- ❖ RV = right ventricle or right ventricular
- ❖ TMT = transient myocardial thickening
- ❖ TVD = tricuspid valve dysplasia
- ❖ UCM = unclassified cardiomyopathy
- ❖ VPC = ventricular premature complex

pressure). To compensate for the decrease in contractility and subsequent decrease in stroke volume, the ventricle (usually the LV) grows larger (eccentric or volume overload hypertrophy, a form of cardiac remodeling) so that the LV end-diastolic internal diameter (LVIDd) and volume increase ('dilate'; Figure 1). As such, the disease is named after the compensatory process ('dilated'), not the primary process, and so DCM is a misnomer. Primary idiopathic myocardial systolic failure would be a more accurate name for the disease in all species, but is cumbersome.

One indelible feature of the disease is reduced contraction (reduced wall motion; reduced fractional shortening/reduced ejection fraction) of the LV. This occurs because the LVIDs is increased and the LVIDd, although increased, is not as increased as the LVIDs. In other words,

Figure 1 Gross pathologic specimen of a heart from a cat with DCM showing the grossly enlarged (dilated) left ventricular (LV) chamber and left atrium (LA). Portions of the LV wall appear thick because it was cut through a papillary muscle



the decrease in contractility leads to a decrease in the amount of contraction of the LV, and the amount of LV remodeling does not have to be as much as the increase in LVIDs to maintain a normal stroke volume. The net result is that the amount the LV wall moves in systole on an echocardiogram (fractional shortening or ejection fraction) is always reduced (Figure 2 and supplementary files 1–3 – see list on page 1065).²

Contraction vs contractility

Note that while contractility and contraction sound similar, they are not synonymous. The amount of wall motion (contraction; fractional shortening/ejection fraction) is primarily determined by contractility, preload and afterload, and so contractility is only one determinant of contraction.

Other cardiac diseases also cause myocardial failure and eccentric hypertrophy. For example, in large dogs and in cats with advanced mitral valve disease causing severe mitral regurgitation, eccentric LV hypertrophy is necessary, again to compensate for the primary disease, and secondary myocardial failure (an increase in end-systolic diameter or volume) is common in the later stages of the disease.³ Consequently, it can be a challenge to distinguish severe primary mitral regurgitation with myocardial failure from DCM in dogs, especially large dogs, where myocardial failure is a more prominent feature. While this also happens in cats, severe primary mitral regurgitation is rare and so this problem, fortuitously, is not often encountered.

Etiology

Currently the etiology of DCM in most cats is unknown (idiopathic). Prior to 1987, the most common cause was taurine deficiency.⁴ More taurine has been added to commercial cat foods since that discovery, so DCM due to taurine deficiency in a cat fed a commercial diet is currently rare to non-existent. However, in the authors' experience, DCM due to taurine deficiency does still occur in cats, primarily those fed home-prepared diets. Cats eating only a single-ingredient diet, for example, a chicken diet, or a vegetarian diet are susceptible to developing taurine deficiency and DCM. It has also been shown that a diet limited to whole, ground-up rabbit produces DCM due to taurine deficiency, likely due at least in part to the fact that rabbit carcasses are deficient in taurine.^{5,6} Therefore, whenever DCM is diagnosed in a cat, a careful diet history should be obtained and, if there is any doubt, plasma and whole blood taurine concentrations should be measured and taurine should be administered (250 mg/cat PO q12h) since DCM due to taurine deficiency is usually a reversible, and therefore curable, disease.⁴

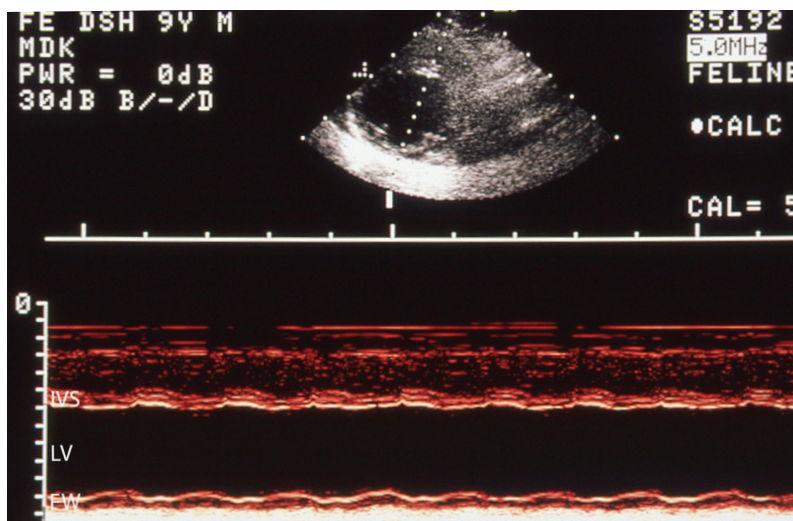


Figure 2 M-mode echocardiogram from a cat with DCM. The left ventricular (LV) end-systolic diameter is markedly increased (22 mm), as is the LV diastolic diameter (25 mm). The interventricular septum (IVS) has no appreciable motion. The LV free wall (FW) motion is markedly reduced. As a result, the fractional shortening is also markedly reduced (12%)


In the past few years, an association has been made between canine DCM and grain-free, legume-rich dog food diets sold by small dog food manufacturers.⁷ In the course of an investigation by the US Food and Drug Administration, a small number of cats eating grain-free diets have also been identified with DCM.⁸ It is unknown whether there is a causal link and, if so, if this is related to taurine deficiency.

Tachycardia-induced cardiomyopathy, which is a reversible form of DCM due to a constant tachycardia, is well described in humans and in experimental dogs.^{9,10} A presumptive, but not definitive, diagnosis of tachycardia-induced cardiomyopathy has been made in two cats.^{11,12} While a heart rate consistently >180 beats per min (bpm) produces tachycardia-induced cardiomyopathy in dogs, the equivalent rate in cats is unknown.

In 30–50% of cases of DCM in humans, a genetic cause can be found.¹³ To date, more than 30 genes are known to cause DCM in humans.¹⁴ Most affected genes code for ion channels, sarcomeres, Z-discs, nuclear proteins and desmosomes but 20% are found in the gene that encodes for titin. Genetic causes of DCM have also been identified in dogs and cattle.^{15,16} While one study performed in a research cattery has suggested genetic involvement, that study was undertaken during a time when taurine deficiency was common.¹⁷ No one has yet found a mutational cause of DCM in cats.

Prevalence

Feline DCM is uncommon to rare. In the authors' estimation, it currently represents <5% of cases of feline cardiomyopathy. As with the other cardiomyopathies, it occurs most commonly in mixed-breed cats.¹⁸



DCM due to taurine deficiency still exists in cats, most commonly in those fed home-prepared, single-ingredient or vegetarian diets.

Natural history

The natural history of the idiopathic DCM in cats seen today is unknown. Only rarely is a diagnosis made prior to the onset of heart failure (subclinical) when the disease is mild to moderate. When heart failure is present the disease is severe (LV fractional shortening <15%).

In research cats fed a taurine-deficient diet, the disease gradually progresses to severe DCM and heart failure over 4–8 months after starting the diet in some, but not all, cats.¹⁹

Once a cat with DCM due to taurine deficiency is started on taurine supplementation, clinical improvement is usually apparent within several weeks.⁴ Echocardiographic improvement, however, lags. It takes 2–3 months before the echocardiogram is markedly improved to normal.

Left atrial (LA) thrombus formation and arterial thromboembolism (ATE) are common in cats with DCM.²⁰

Presentation and diagnosis

Almost all cats with DCM present in left heart failure (ie, with pulmonary edema [PE] and/or pleural effusion [PLE]), although right heart failure (ascites) can occur.²¹ Presenting signs for cats with DCM in left heart failure are the same as those of cats in left heart failure due to other cardiomyopathies. Tachypnea, dyspnea and hypothermia predominate.¹⁸ Hypothermia (low core temperature) is attributed to a low cardiac output (poor perfusion); the ears and paws are often also cool. On auscultation, a gallop sound is common, but a heart murmur is heard in fewer than half the cases. Arrhythmias are uncommon. Radiographically the cardiac silhouette is indistinguishable from that of cats with other forms of cardiomyopathy.²² The plasma concentrations of amino terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTn I) have not been systematically evaluated in cats with DCM but are likely elevated.

The definitive clinical diagnosis of feline DCM depends on echocardiography. The most noticeable abnormality in a cat presented in heart failure is a very poorly contracting LV (Figure 2 and supplementary files 1–3). The LVIDs and LV volume are usually markedly increased due to compensation for the decrease in myocardial contractility. The LVIDd and LV volume are also usually severely increased but less so than the increase in LVIDs and volume. The net result is a low LV fractional shortening ($(LVIDd - LVIDs) / LVIDd$; the measurement of the amount of LV myocardial contraction), which, in the authors' experience, and as stated earlier, is uniformly <15% in cat in heart failure due to DCM.

The LA is usually severely (but occasionally moderately) dilated. There is often functional mitral, and sometimes tricuspid, regurgitation (Figure 3 and supplementary file 3).

Prognosis

The long-term prognosis for a cat in heart failure due to DCM that is not related to taurine deficiency is grave. Idiopathic DCM is uniformly a terminal disease in cats. Some cats die during hospitalization. The rest most commonly die within a few weeks to a few months after diagnosis.¹⁸ Hypothermia is a poor prognostic sign.¹⁸

The short-term prognosis for a cat with DCM due to taurine deficiency is guarded. It is common for those cats to die during the first few weeks after diagnosis. However, if a cat can be successfully treated in the hospital and survive for several weeks at home on taurine supplementation, most will survive and return to normal (ie, long-term prognosis improves dramatically).²³

Treatment

Treatment of a cat presenting with severe heart failure due to DCM is similar to that for a cat with severe heart failure due to hypertrophic cardiomyopathy (HCM) (see Part 2). Thoracocentesis is required if severe PLE is present (see Part 1). Parenteral furosemide administration (2–4 mg/kg IV q1–4h initially) is needed to treat tachypnea and dyspnea due to severe PE when a cat is presented on an emergency basis. In theory, positive inotropic support with dobutamine or dopamine should be beneficial, but no studies have documented whether it is, nor whether arrhythmogenesis is a problem. The administration of oral or parenteral pimobendan (0.625–1.25 mg/cat PO q12h) could also be considered.^{18,24}

A potent parenteral vasodilator, such as nitroprusside, is commonly used in humans with a similar presentation (cold [hypothermia] and wet [pulmonary edema]).²⁵ This is rarely tried in cats, perhaps due to the low incidence of DCM in cats, cost of nitroprusside, contraindication in hypotension, heightened concerns in cats around the adverse effects of nitroprusside reported in humans (methemoglobinemia, cyanide toxicosis),²⁶ or some combination of these or other factors.

In theory, intravenous fluid therapy is contraindicated in a cat with severe PE (see Part 1). It certainly makes little sense to administer a

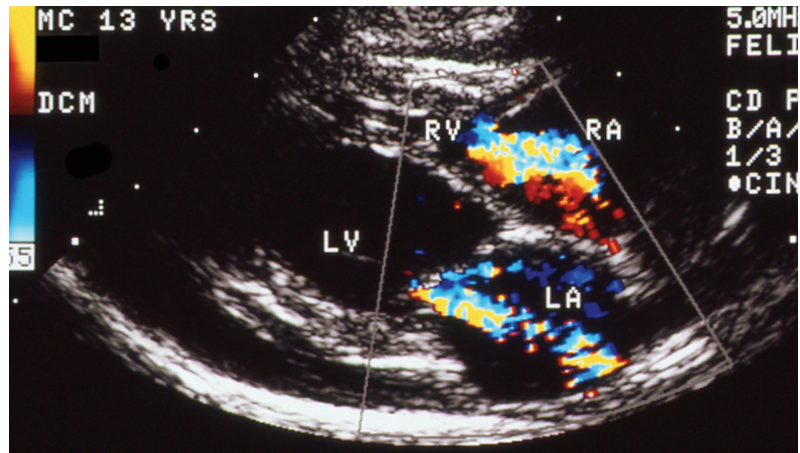


Figure 3 Right parasternal long-axis color flow Doppler echocardiographic view of a heart from a cat with DCM. There is functional regurgitation of both the tricuspid (upper) and mitral (lower) valves in systole. There is also pleural effusion present. RA = right atrium; LA = left atrium; LV = left ventricle; RV = right ventricle

Parenteral, high-dose loop diuretic administration is crucial in cats with severe pulmonary edema presented for emergency evaluation. The dosage should be judiciously tapered as soon as unmistakable, substantial improvement is apparent in the cat's RR and effort.



loop diuretic and IV fluids simultaneously. But, unlike dogs, cats commonly become dehydrated with intensive diuresis and refuse to eat or drink. If that happens, diuretic therapy may need to be discontinued for a short time and parenteral fluids administered. This backtracking after excessive diuretic administration becomes challenging both for patient management and for client communication, and the preferred approach is to try to avoid it. Therefore, while intensive diuretic administration is usually required in acute heart failure, transitioning to judicious tapering of the diuretic dosage should be undertaken as soon as an unmistakable, substantial improvement is apparent in the cat's respiratory effort, respiratory rate (RR) and demeanor. Several credible anecdotal reports describe successful management of fluid balance in cardiomyopathic cats using enteral hydration (eg, via nasogastric tube), and this approach deserves further investigation.

Once a cat has responded to treatment and is clinically and hemodynamically stable (breathing and behaving more normally), it should be sent home as soon as possible with oral loop diuretic therapy (required for life). Dosages are the same as outlined for HCM (see Part 2). An angiotensin-converting enzyme inhibitor can be administered but there is no proof that this is beneficial. Pimobendan can also be administered. In one case series, pimobendan administration was associated with longer survival in cats with idiopathic DCM, but survival only increased from an average of 12 days without the drug (range 1 to >502 days) to 49 days with pimobendan (range 1–244 days; *P* = 0.048) and the study was retrospective, meaning the results do not account for the numerous other factors that can influence survival time.¹⁸ It may make sense to administer pimobendan

It makes little sense to administer a loop diuretic and IV fluids simultaneously.

during the first several weeks after a diagnosis of DCM due to taurine deficiency while waiting for the myocardium to respond to taurine supplementation; however, since it is, at best, only a mild positive inotrope in cats, one should probably not depend on it to provide benefit. Spironolactone administration can also be considered.²⁷ Given that cats with DCM and heart failure uniformly have atrial enlargement, clopidogrel treatment is, in the authors' opinion, also warranted (see Part 2).

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is characterized by isolated LV diastolic dysfunction due to endocardial, subendocardial or myocardial fibrosis.²⁸ However, systolic myocardial dysfunction (DCM) has occasionally been reported either in association with, or due to, RCM.²⁹ This shows the imperfection of current systems of classification that categorize the left-sided cardiomyopathies into mutually exclusive entities (HCM, RCM, DCM) when individual cats may show features of two or maybe even all three.

As described in Part 2, diastolic dysfunction implies a stiffer (less compliant) than normal ventricle (usually the LV). A stiff LV means there is an increase in LV diastolic intraventricular pressure for any given intraventricular volume. For example, it takes more force (pressure) to distend a balloon made of rubber than it does one made of latex, and the LV in a cat with RCM is more like rubber. Since the mitral valve is open in diastole, the high diastolic LV pressure is transmitted back into the LA causing LA enlargement and left heart failure. In other words, the fluid continuity of the circulation from the lungs to the left side of the heart means that LV diastolic, LA diastolic, and pulmonary venous, pulmonary capillary and pulmonary artery diastolic pressures are essentially the same. The high pulmonary capillary hydrostatic pressure forces fluid through the pulmonary capillaries and into the interstitium in an amount that exceeds the lymphatic system's ability to clear it, producing PE and/or PLE (left heart failure). Although the right atrium (RA) may also be enlarged, right heart failure (ascites) is rare.³⁰

HCM is also characterized by diastolic dysfunction due to myocardial fibrosis. The difference is that HCM has myocardial thickening (concentric hypertrophy) while RCM does not. With RCM the fibrosis is also probably more severe.



RCM has been subcategorized into distinct forms. These forms reflect the structural changes observed echocardiographically and at necropsy, but are not known to evolve differently over time, to carry different prognoses, nor to respond differently to treatment. Recognized forms of RCM are the endomyocardial form (endomyocardial fibrosis), the myocardial form, endomyocarditis/endocardial fibrosis and endocardial fibroelastosis.^{30–32}

✦ The endomyocardial form is characterized by macroscopically visible deposition of fibrous tissue that may diffusely involve the LV (diffuse form) or appear as a thick, discrete crescent or band of fibrous tissue that bridges the interventricular septum and LV free wall and/or papillary muscles (patchy form).³² In the patchy form, the band of excessive fibrous tissue is sometimes referred to as an endomyocardial scar, but this term can be misleading. The 'scar' in endomyocardial RCM is a protruding shelf or dense network of tissue that tethers segments of the LV walls to each other (Figure 4 and supplementary files 4–6).

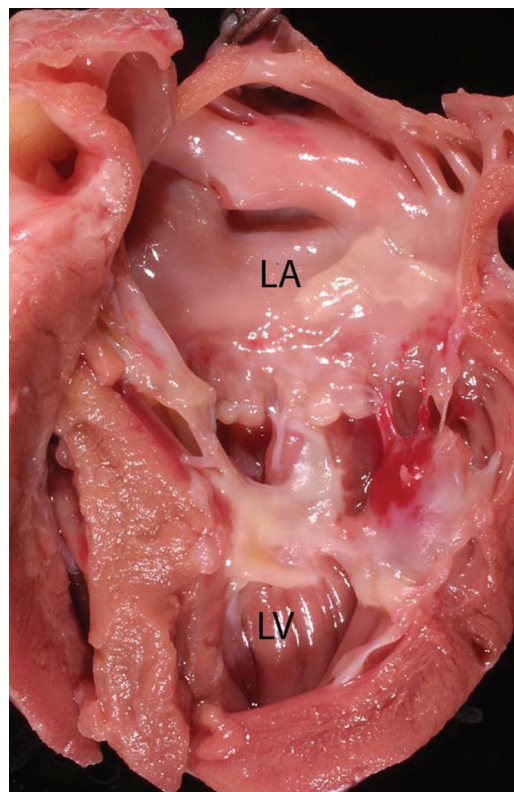


Figure 4 Gross pathologic specimen of a heart from a cat with the endomyocardial form of RCM. There is fibrous tissue (white material in the left ventricle [LV]) bridging the interventricular septum, left ventricular free wall and papillary muscles. LA = left atrium

Diastolic dysfunction due to cardiac fibrosis occurs with both HCM and RCM, but with HCM the fibrosis occurs secondarily to the LV wall thickening while in RCM it is the primary lesion.

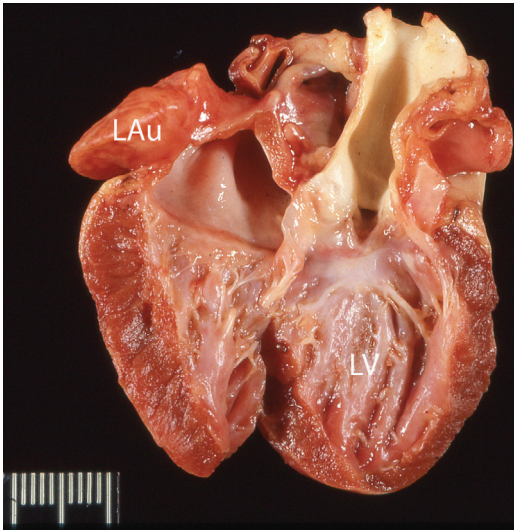


Figure 5 Gross pathologic specimen of a heart from a cat with endomyocarditis/endocardial fibrosis. The left auricle (LAu) is markedly enlarged. The endocardium of the left ventricle (LV) is thick and white. The LV wall thickness is within normal limits

- ❖ In the myocardial form there is primarily replacement fibrosis (cells have died and been replaced by scar tissue) in the myocardium.³⁰
- ❖ With endomyocarditis/endocardial fibrosis, the endocardium is either inflamed (neutrophils and macrophage infiltrate, most commonly) and fibroplastic or fibrous (Figure 5).³¹
- ❖ Endocardial fibroelastosis is characterized by endocardial thickening due to increased fibrous/elastic tissue. It has only been described in Burmese cats in the 1980s and in one family of research cats in 1994.^{33,34}

Etiology

The etiology of feline RCM is, for the most part, unknown. The endomyocarditis/endocardial fibrosis complex was described in 1995.³¹ Most of the cats in that study with endomyocarditis (n = 37) also had an interstitial pneumonia. This suggested that the problem was due to an infectious agent. Additionally, it was proposed that the cats with endocardial fibrosis had a more mature form of the same disease. In 2018, a study of cats with similar findings (although 70% had suspected HCM also) found evidence of *Bartonella* organisms in the endomyocardium of half the affected cats.³⁵ Half the cats also had an interstitial pneumonia.

The lesions in the patchy version of the endomyocardial form of RCM likely follow false tendons and so it is possible an infectious agent might be involved that has an affinity for this type of tissue.³⁶

Endocardial fibroelastosis has been identified in one breed (Burmese) and one cat family, and so is likely heritable.³⁷ Interestingly, in humans the mumps virus may be a cause of endocardial fibroelastosis.³⁸

In humans, some patients with the myocardial form of RCM have genetic mutations that are thought to be responsible for the disease. One of the more common genes involved is cTn I.^{39,40} No one has yet published findings regarding a genetic mutation in cats with RCM.

Natural history and presentation

The endomyocardial form of RCM mostly affects mixed-breed cats.³⁶ There is no apparent sex predilection. The age range in one study was 4 months to 19 years.³⁶

The natural history of feline RCM during the subclinical phase of the disease is unknown. It is rarely diagnosed prior to the onset of heart failure or ATE, likely in part because the lesion does not inherently produce turbulent blood flow and thus is usually silent (no murmur). Furthermore, since atrial enlargement is part of the echocardiographic diagnostic criteria of RCM, early (eg, stage B1) disease could not be recognized using current two-dimensional (2D) echocardiographic criteria. In three case series, 83–91% of cats with RCM presented for signs referable to heart failure.^{30,36,41} In one of these studies, 10% of affected cats had ascites.⁴¹ Hindlimb paresis or paralysis due to ATE is reported variably (7%, 12%, 14% and 41% in four case series of cats with RCM),^{30,36,41,42} but ATE may be underreported if, historically, a nonspecific unclassified cardiomyopathy (UCM) category included RCM cases.⁴³ In the authors' experience, signs of ATE are an all too familiar initial manifestation of RCM in cats. A few cats with RCM have mild pericardial effusion identified incidentally on echocardiography.

Physical examination

Most physical examination findings in cats with RCM are similar to those of cats with other cardiomyopathies at equivalent stages.⁴¹ A systolic heart murmur may or may not be common. In one study it was not mentioned, in another only 10% had a murmur, while in another 77% of cats had a murmur.^{30,41,42} In one study a gallop sound was present in 31% and an arrhythmia in 23%.⁴² Dyspnea is a frequent finding, with retrospective studies reporting it in 83–87% of cats with RCM.^{36,41,42}

Most physical examination findings in cats with RCM are similar to those of cats with other cardiomyopathies at equivalent stages.



Diagnosis

The diagnosis of feline RCM is dependent on 2D and Doppler echocardiography.^{41,42} The hallmark 2D features of the myocardial form are a grossly normal-appearing LV (structurally normal and functionally normal in systole on an echocardiogram) with a large LA. The RA may also be increased in size. Historically, any cat with a normal-appearing LV and LA enlargement could have been considered to have RCM. However, such changes can exist in cats with normal diastolic LV filling, and such cats by definition do not have RCM.⁴⁴ Therefore, to make a definitive diagnosis of RCM requires identifying diastolic dysfunction in the absence of HCM. Pulsed wave Doppler interrogation of mitral inflow can be used for this purpose and may reveal a tall E wave (increased early inflow velocity; restrictive filling pattern) if the heart rate is slow enough (<180 bpm) that the E and A waves are not summated (fused).^{30,41,42} If the E and A waves are summated, one can wait for the heart rate to come down as the cat relaxes over time, can apply a vagal maneuver, such as pressing on the nasal planum, or can administer a low dose of a beta blocker, such as ocular timolol, to slow the heart rate.^{45,46} Tissue Doppler interrogation of the mitral valve annulus can also be performed and should show a reduced E' wave velocity.⁴⁷

Thoracic radiographs in dyspneic cats that have RCM show a higher occurrence of PLE (59%) than PE (25%) but both can be present (16%).⁴¹ A left auricular bulge is commonly present on a ventrodorsal radiograph in a cat in left heart failure, if the cardiac silhouette is visible.

Cardiac arrhythmias are well recognized in affected cats. Supraventricular tachyarrhythmias have been documented in 7–34%, and ventricular arrhythmias in 0–29%, of cats with RCM in four case series.^{30,36,41,42} On Holter monitoring, ventricular arrhythmias predominate (median 803 ventricular premature complexes [VPCs]/24 h; median 45 supraventricular complexes/24 h).⁴⁸

With endocardial fibrosis and endocardial fibroelastosis the endocardium may appear hyperechoic.³¹ This is a subjective assessment and thus is prone to over- or under-interpretation. The LA is enlarged. Doppler findings are the same as for the myocardial form. A severely enlarged LA (left atrial diameter to aortic root diameter ratio >2) is common and confers a poor prognosis.⁴²

The endomyocardial form of feline RCM is the easiest to identify.³² In most cases of the patchy form, a thick shelf or band of fibrous tissue spanning the LV is apparent (Figure 6 and supplementary files 4–6),⁴⁹ although identifying such a structure may require advanced

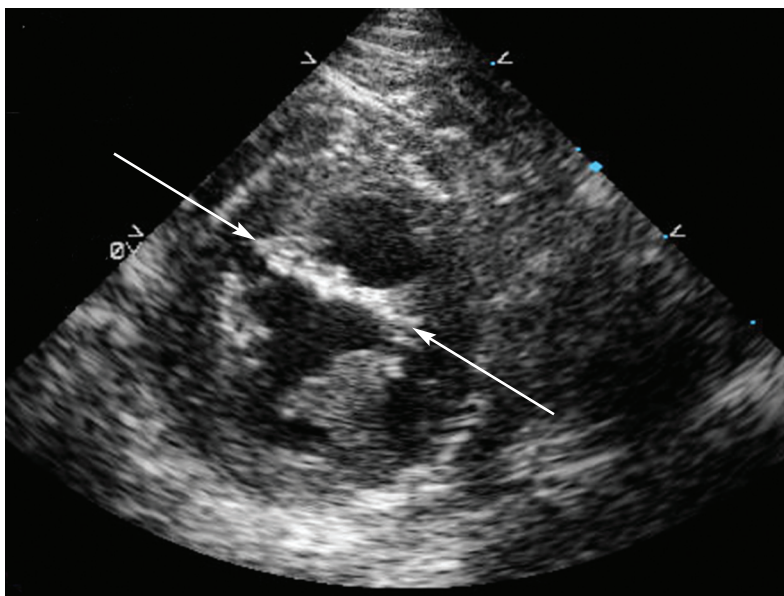


Figure 6 Right parasternal short-axis echocardiographic view of the left ventricle in a cat with the endomyocardial form of RCM. There is a dense fibrous band (between the arrows) spanning the left ventricle

In most cases of the patchy endomyocardial form of feline RCM, a thick shelf or band of fibrous tissue spanning the LV is apparent.



To make a definitive diagnosis of RCM requires identifying diastolic dysfunction on an echocardiographic examination in the absence of HCM.

echocardiographic training to differentiate it from obliquely imaged normal structures. The LA is enlarged. Doppler findings are the same as for other forms of RCM.

Prognosis

Most cats with RCM present in left heart failure.⁴² A few have right heart failure (ascites). In one study, cats with RCM that presented without respiratory distress had a significantly longer median survival time (466 days) compared with those with RCM and respiratory distress (64 days).⁴¹ The prognosis is poor for cats in heart failure with any form of RCM. In one study, the median survival time was only 30 days.³⁶ In another it was 69 days.⁴¹ Some cats present with ATE, often with dramatic atrial enlargement and spontaneous echocardiographic contrast.⁴¹ Sudden death is possible.⁴²

Treatment

Treatment of RCM is essentially the same as for HCM (see Part 2). Heart failure is treated with a loop diuretic. Pimobendan appears to be safe but no prospective clinical trials have been performed to assess efficacy.^{50–52} When the LA is severely enlarged, clopidogrel, clopidogrel plus aspirin, or an oral, selective factor Xa inhibitor (eg, apixaban or rivaroxaban) alone or along with clopidogrel is indicated to try to prevent ATE.⁵³

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is rare in cats and is a very different disease to that seen in dogs (primarily Boxer dogs). Pathologically, feline ARVC behaves similarly to ARVC in humans. It is characterized anatomically by marked thinning (myocardial atrophy) of the right ventricular (RV) free wall.⁵⁴ This can be diffuse or regional (aneurysmal). It is common for regions of the RV free wall to be nearly or completely replaced by fibrous or fibrofatty tissue. On necropsy the affected regions of the free wall are often so thin as to be translucent (Figure 7). The RA is usually severely enlarged.

The age range for cats presenting with ARVC is 1–20 years.⁵⁴ Most are mixed-breed cats.

Etiology

The cause of feline ARVC is unknown. In humans it is usually a heritable disease, most commonly caused by mutations in genes that encode for proteins in the desmosome.⁵⁵ To date, no cat families have been identified with ARVC and no genetic analysis has been reported.

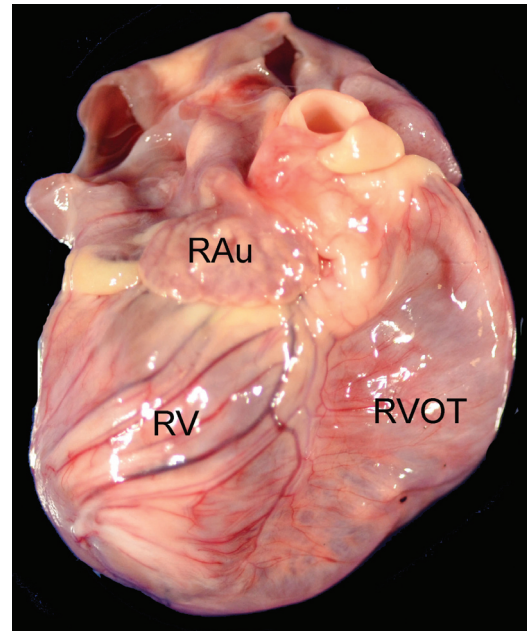
Natural history

The natural history of subclinical feline ARVC is unknown, as this stage of the disease has not been identified nor studied. Cats present to a veterinarian with end-stage ARVC, most commonly in right heart failure (ascites; PLE).⁵⁴ In cats with ascites due to right heart failure the caudal vena cava and hepatic veins are enlarged (supplementary file 7). Syncope and sudden death can occur but sudden death does not appear to predominate as it does in humans, although it may be underreported in cats.^{56,57} Arrhythmias are common on electrocardiography (ECG) and consist of VPCs, ventricular tachycardia, atrial premature complexes, atrial tachycardia and atrial fibrillation.^{48,54} Tricuspid regurgitation is invariably present and usually creates a right-sided systolic heart murmur. Mural thrombosis in the RV and the LA, which could lead to pulmonary thromboembolism and ATE respectively, has been described.⁵⁴

Diagnosis

On echocardiography, the RA and RV chambers are markedly enlarged (Figure 8 and supplementary files 8 and 9).⁵⁴ Tricuspid regurgitation is present on color flow Doppler echocardiography. Regions of aneurysmal akinesis (lack of movement) of the RV free wall can be identified in some cats and are strongly supportive of ARVC. The motion of

Figure 7 Gross pathologic specimen from the same cat as shown in the videos of supplementary files 8 and 9. The right ventricular wall that covers the body of the right ventricle (RV) and the right ventricular outflow tract (RVOT) is devoid of myocardium and so is translucent. Myocardium (presumably that of the interventricular septum) can be seen through it. Coronary vessels are unaffected and can be seen coursing through the RV free wall that covers the body of the RV. The right auricle (RAu) is enlarged. Courtesy of Ashley N Sharpe, DVM



The primary differential diagnosis for ARVC is tricuspid valve dysplasia.

the interventricular septum may be paradoxical. The LV is normal to small, but the LA is enlarged in some cats.

The primary differential diagnosis is tricuspid regurgitation due to tricuspid valve dysplasia (TVD). Often it is not easy to distinguish between the two conditions. Both can be identified in young and old cats; RV free wall thinning and aneurysms are not always present in cats with ARVC and, even when present, are often not easily identified; the tricuspid valve is not always obviously abnormal on an echocardiogram in cats with TVD; both diseases cause tricuspid regurgitation; and both diseases result in right heart failure.

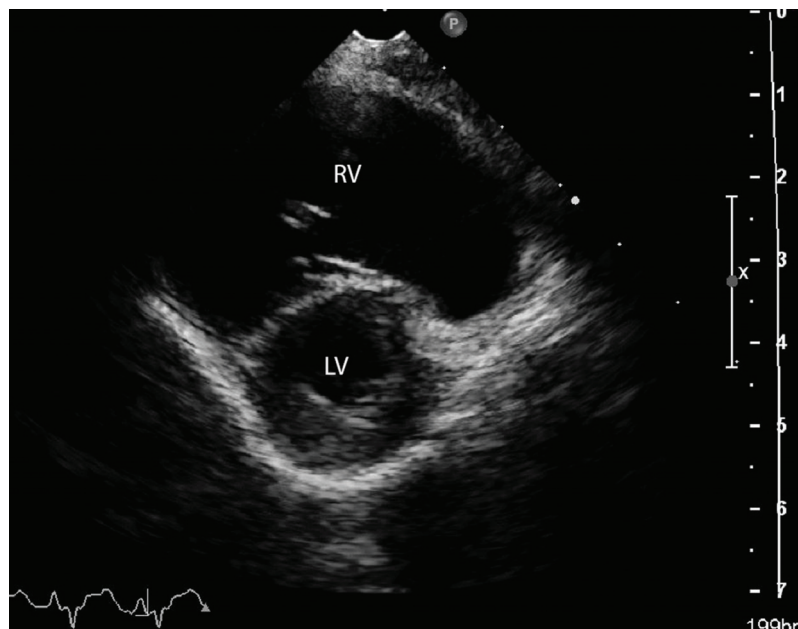


Figure 8 Right parasternal cross-sectional echocardiographic view of the left ventricle (LV) and grossly enlarged right ventricle (RV) from a cat with ARVC. Courtesy of Ashley N Sharpe, DVM

However, in some cats with TVD the RV free wall is obviously hyperdynamic and in some the tricuspid valve is obviously malformed.⁵⁸ In cats with ARVC it may be possible to see that the RV free wall is not moving or is barely moving (akinetic or hypokinetic) (Figure 9). In early diastole the tricuspid valve will usually open wide in a cat with TVD due to the marked amount of regurgitant blood volume re-entering the RV in early diastole, whereas it may open less than normal in a cat with ARVC. Still, the distinction is not possible without necropsy in some cases.

Prognosis

The long-term prognosis is poor for cats in heart failure due to ARVC.⁵⁴

Treatment

Treatment is non-specific and palliative. A loop diuretic is required for any cat in heart failure due to ARVC and is usually administered for life. Thoracocentesis must be a part of the initial management of any cat with large-volume PLE. PLE often does not respond well to diuretic therapy and so periodic thoracocentesis is often needed over the longer term. Similarly, abdominocentesis is required for any cat with severe ascites.

There are limited data describing the use of pimobendan in four cats with right heart failure due to end-stage ARVC;⁵⁹ pimobendan is not known to be arrhythmogenic in cats and so could be tried.⁵⁹



PLE often does not respond well to diuretic therapy and so periodic thoracocentesis is often needed.

Ventricular tachycardia likely predisposes a cat with ARVC to sudden death. Sotalol (10–20 mg/cat PO q12h) may be indicated in cats with this ECG finding.

The ventricular rate in a cat with fast (>200 bpm) atrial fibrillation should be slowed with either diltiazem, a combination of digoxin and diltiazem, or sotalol.

Left ventricular noncompaction

Left ventricular noncompaction (LVNC) is a form of cardiomyopathy described in humans that is characterized by trabeculations in ventricular, usually LV, myocardium.⁶⁰ It has also been reported in one cat.⁶¹ This cat was a mixed-breed cat from a research colony that had the A31P mutation known to cause HCM in Maine Coon cats. The A31P mutation is also known to cause LVNC in humans.⁶² Increased awareness may allow this form of cardiomyopathy to be diagnosed in other cats in the future.

During early fetal development, prior to the development of the coronary vasculature, the LV myocardium is heavily trabeculated. This rippled or corrugated configuration increases the surface area of the endocardium to allow more oxygen to penetrate the myocardium.⁶³ Once the coronary vasculature is developed, the myocardium undergoes compaction (loss of trabeculation). LVNC is thought to be due to the failure of the myocardium to undergo compaction. This results in an outer, subepicardial layer of normally compacted myocardium and an inner, subendocardial layer of noncompacted myocardium.

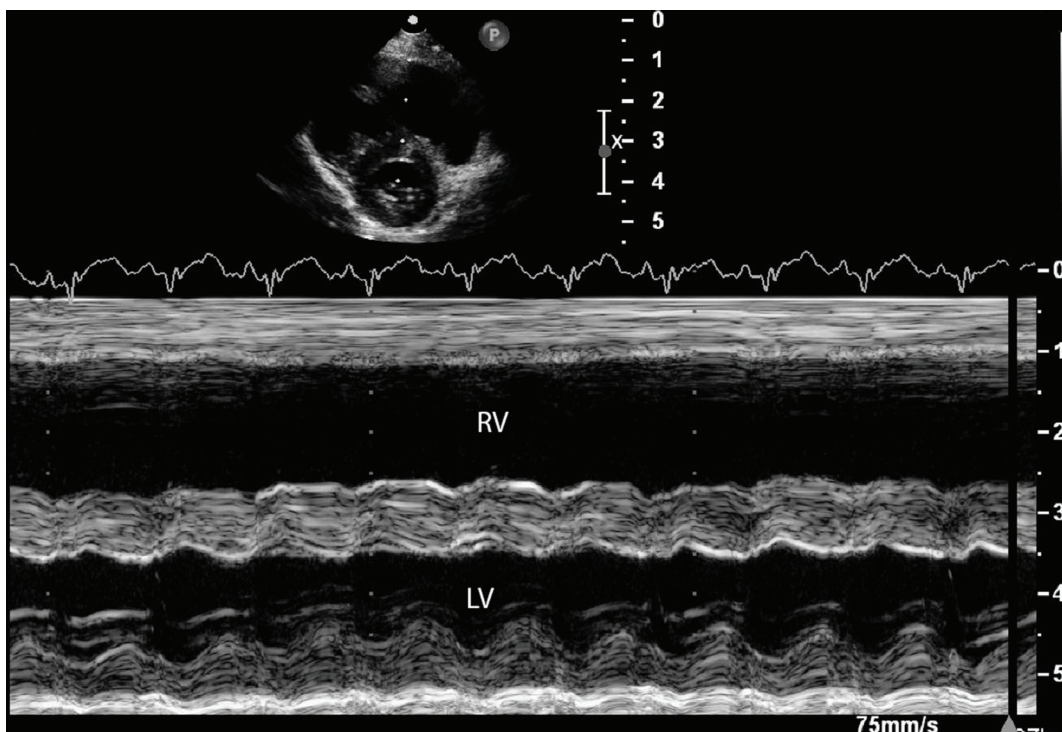


Figure 9 M-mode echocardiogram from the same cat as in Figure 8. Note that there is no right ventricular (RV) free wall motion (across to the left from the 1 cm mark). LV = left ventricle

Numerous, excessively prominent trabeculations and deep intertrabecular recesses are found in the mid-ventricular and apical regions of the LV in a cat with LVNC.



Etiology

In humans, the etiology is either genetic or idiopathic. Approximately 30% of human cases are caused by mutations in the myosin heavy chain gene or the myosin binding protein C gene.^{64,65} The one reported cat had a mutation (A31P) in the feline myosin binding protein C gene.⁶¹ LVNC has been reproduced in mice by altering the Notch system.⁶⁶

Natural history

The natural history of LVNC is unknown in cats. In humans it can be diagnosed at any age; it is often subclinical but can cause heart failure, arrhythmias and sudden death.⁶⁰

Diagnosis

Echocardiography is the primary diagnostic tool. Numerous, excessively prominent trabeculations and deep intertrabecular recesses are found in the mid-ventricular (especially caudal and lateral segments) and apical regions of the LV (supplementary files 10–14).⁶⁷ The non-compacted myocardium appears as recesses/trabeculae that communicate with the LV cavity in a long-axis echocardiographic view and appears spongiform (like Swiss cheese) in a cross-sectional (short-axis) view.⁶⁸ To make the diagnosis, direct blood flow from the ventricular cavity into the deep intertrabecular recesses should be documented using color Doppler echocardiography. The ratio of noncompacted to compacted layers should be >1 or >2 , depending on the criteria used.^{69,70}

Prognosis

The prognosis is unknown in cats. The value of identifying LVNC in cats may lie in its association with other genetic disorders, as in humans, or in a distinct biological behavior, response to treatment or prognosis. These possibilities are speculative in cats currently.

Treatment

Treatment depends on clinical signs and the presence or absence of atrial enlargement, and is the same as for other cardiomyopathies.



Some cases of NCM might represent transition phases from one cardiomyopathy phenotype to another or may represent the existence of two forms of cardiomyopathy in the same heart.

Cardiomyopathy – nonspecific phenotype

Not all non-congenital structural cardiac disease in cats fits into the aforementioned categories. Abnormalities include everything from a normal LV with a large LA but normal LV diastolic function using Doppler echocardiography to a grossly malformed LV that defies simple categorization (supplementary files 15–18). These cardiac changes have typically been grouped into the class called unclassified cardiomyopathy (UCM), a term borrowed from human medicine.⁷¹ However, specific types of heart diseases are usually placed into the UCM category in human medicine. For example, LVNC is still considered a UCM by the World Health Organization but is in its own class in the American Heart Association system.^{72,73}

An alternative classification system – morphofunctional phenotype, organ involvement, genetic inheritance pattern, etiology, functional status (MOGE[S]) – has more recently been proposed that includes the term cardiomyopathy – nonspecific phenotype (NCM).⁷⁴ The advantage of this term over UCM is that it invites the examiner to describe the specific abnormality or abnormalities noted, instead of just placing all types of abnormalities into one UCM basket without describing the structural changes.²⁴

Some cases of NCM may represent transition phases from one cardiomyopathy phenotype to another or may represent the existence of two forms of cardiomyopathy in the same heart, as seen in Norwegian Forest Cats.⁷⁵

Since cardiomyopathies are prevalent in cats, it is not unusual for other forms of heart disease, such as congenital heart disease or acquired valvular disease, to be mistaken for a cardiomyopathy and to be erroneously placed in this nonspecific category.

Natural history

Most of these cats present with a large LA and in left heart failure or with ATE. Right heart failure is rare.

Diagnosis

The diagnosis of NCM is made using echocardiography in cats with abnormalities that do not fit into the traditional categories of HCM, DCM, RCM, ARVC or LVNC. Care must be taken to describe, in detail, the specific echocardiographic abnormalities identified. As for other cardiomyopathies, the size of the LA is generally key to determining prognosis. Results

of Holter monitoring in cats with NCM are similar to those of other feline cardiomyopathies.⁴⁸

Prognosis

When a cat with NCM has heart failure or an ATE, the prognosis is considered the same as for any other feline cardiomyopathy.

Treatment

Treatment depends on clinical signs and is the same as for other cardiomyopathies.

Myocarditis

At the present time, feline myocarditis appears to be rare. Technically myocarditis is not a cardiomyopathy, but it can mimic the anatomical appearance and the altered function (phenotype) seen with the feline cardiomyopathies, including HCM, RCM and DCM. One example from the literature is a cat with coronavirus infection that had granulomas in the myocardium which caused LV wall thickening and so had the echocardiographic appearance of HCM.⁷⁶ *Bartonella* species infection, as a cause of feline endomyocarditis or playing a causative role in transient myocardial thickening (TMT; see Part 2), would be an additional prime example.^{35,77} Feline transmissible myocarditis and diaphragmitis was reported as a phenomenon in 1993.⁷⁸ More recent evidence suggests it may also be due to *Bartonella henselae*.⁷⁹ There is one report of cats with HCM and myocarditis where evidence of feline immunodeficiency virus was found in the myocardium.⁸⁰ This was not found in cats with HCM alone.

Heart failure associated with corticosteroid administration

Numerous anecdotes and some case series exist regarding an association between corticosteroid administration and left heart failure in cats. However, very little documentation of this phenomenon is present in the literature. Most of the described cases follow a similar pattern – a cat is presented to a veterinarian, a corticosteroid is administered (most commonly a long-acting injectable form) and within several days to a week or two the cat re-presents in respiratory distress with radiographic evidence of PE and possibly PLE.

There is one retrospective study from 2004 in the literature that describes 12 cats that fit the scenario just described.⁸¹ In that study, parenteral methylprednisolone acetate (12–24 mg IM) had been administered to eight cats, with the other four being given a short-acting oral or parenteral corticosteroid. Cats presented with respiratory distress between 1 and 19 days after drug administration. A corticosteroid had been administered to four of the cats

previously with no untoward effect. Heart rate was <150 bpm in eight cats. All cats were tachypneic and at least half were hypothermic. Systolic blood pressure was reported to be low (<100 mmHg) in all cats. All 12 cats had PE while nine also had PLE. Total serum thyroxine concentration was measured in seven cats and was not elevated in any and was low in five. An echocardiogram was obtained for 11 of the cats.

Only population characteristics are provided in the 2004 manuscript, but some general assessments can be made. While most of these cats had findings consistent with HCM (ie, an LV wall thickness >6 mm), there were some that did not. LA diameter ranged from 15 to 23 mm, which means the LA size ranged from normal to severely enlarged. All cats were treated with furosemide and oxygen support. Seven survived to hospital discharge and were long-term survivors (366 to >2000 days). These cats were re-examined periodically, and all were weaned off furosemide anywhere from 36 to 1563 days later. Echocardiographically, the thickness of the LV decreased significantly for this population of cats and the LA returned to a normal size in each cat over time.

This problem is a conundrum. Is the left heart failure due to corticosteroid administration, due to stress (eg, being seen by a veterinarian) or due to both? If it is due to the corticosteroid, does the corticosteroid cause LV wall thickening that leads to left heart failure or do these cats already have HCM, which the corticosteroid exacerbates; alternatively, does the corticosteroid increase blood volume (eg, cause translocation of free water from the intra- to extracellular compartments, or cause renal sodium and water retention) and that is responsible for heart failure? Why is the LA not at least moderately enlarged in all cats? Is the condition truly reversible? If it is, how does it relate to TMT?

To examine the theories that a corticosteroid may increase blood volume and LV wall thickness, methylprednisolone acetate (5 mg/kg IM) was administered to 12 cats in one study.⁸² At 3–6 days following administration, this resulted in increases in blood glucose and plasma volume and decreases in serum sodium and chloride concentrations and in hematocrit, red blood cell count and hemoglobin concentration. The plasma volume increased dramatically, by more than 40%, in three cats. LV wall thickness increased, on average, by 1 mm. The authors speculated that the increase in plasma volume was caused by insulin antagonism by the corticosteroid, leading to hyperglycemia, which in turn drove an osmotic shift of free water from the intra- to the extracellular spaces. However, in the present authors' opinion, this seems unlikely since the apparent calculated increase in osmolality was small.

Numerous anecdotes and some case series describe an association between corticosteroid administration and left heart failure in cats. Caution, especially with the administration of methylprednisolone acetate, is probably warranted.



Based on these limited data, it is at least plausible that methylprednisolone acetate might increase blood volume dramatically in some cats and that this could cause heart failure in a cat with an underlying subclinical cardiomyopathy. Further studies are warranted to see if this is replicable. There are additional questions still to ponder. Could methylprednisolone acetate cause TMT? If methylprednisolone acetate can do this, can other corticosteroids do this also? If this phenomenon is real, why does it occur in some cats and not in others?

Since subclinical cardiomyopathy in cats is often undetectable and since it is not feasible to perform an echocardiogram on every cat prior to administering a corticosteroid, this problem (identifying a susceptible cat prior to corticosteroid administration) is probably not resolvable in widely applicable and practical terms. In theory, NT-proBNP and/or cTn I determinations, particularly using a point-of-care test, could be evaluated prior to corticosteroid administration to a cat. How well might this help avoid complications like heart failure? A clinical trial would need to be undertaken to answer that question. Since the problem is uncommon, it is likely that such a clinical trial would need to enroll a very large number of cats and so would be expensive. In the interim, caution, especially with the administration of methylprednisolone acetate, is probably warranted and owners should be warned about possible complications and counseled on signs to watch for (eg, tachypnea – an increase in the sleeping RR in the subsequent days to weeks) before corticosteroid administration.

Endocrinopathies and heart disease in cats

Hyperthyroidism

Hyperthyroidism is the most common endocrine cause of feline cardiac disease (hyperthyroid heart disease).⁸³ While it can cause changes on its own, it also exacerbates and complicates existing heart disease/failure. While no one has prospectively evaluated how the onset of hyperthyroidism changes echocardiographic variables in cats, changes in these variables have been examined as cats return to a euthyroid state after treatment for hyperthyroidism.^{84–87}

Because hyperthyroidism produces an increased metabolic rate and so an increased demand for oxygen delivery to the tissues, an increase in cardiac output (heart rate x stroke volume) is necessary. Therefore, one might expect both an increase in heart rate and an increase in stroke volume with hyperthyroidism. An increase in stroke volume can be attained by an increase in LV end-diastolic diameter, a decrease in LV end-systolic diameter (both would cause an increase in fractional shortening), or both. While an increase in heart

rate is reasonably uniform in cats with hyperthyroidism, there are no consistent changes in LV diastolic diameter or fractional shortening. In some cats the diastolic diameter is increased but more commonly it is normal. In many, the fractional shortening is increased but in some it is normal. In a large percentage of cats neither is abnormal. The type and degree of these changes has no apparent relationship to serum total thyroxine concentration.⁸⁵

While an increase in LV wall thickness does not produce a hemodynamic advantage, apparently thyroxine does stimulate LV concentric hypertrophy in many, but certainly not all, cats based on the fact that the LV wall becomes thinner in many hyperthyroid cats after successful treatment.⁸⁵ In general, this reduction is on the order of 1–2 mm. Consequently, it is likely that hyperthyroidism increases LV wall thickness by ≤ 2 mm in many cats. As such, if a cat with hyperthyroidism is found to have severe LV hypertrophy (diastolic LV wall thickness ≥ 7 mm) on an echocardiogram, it is unlikely all that hypertrophy is due to the hyperthyroidism. Rather, it is more likely the cat either already had severe HCM and thyrotoxic cardiac changes were minimal, or had mild to moderate HCM that was exacerbated by the hyperthyroidism.

Hyperthyroidism exacerbates heart failure by increasing the basal metabolic rate.⁸⁸ Therefore, heart failure is easier to manage once hyperthyroidism is controlled. An additional advantage in some cats is that the LV hypertrophy might partially regress, and so diastolic function might improve. Regardless, it is imperative to control hyperthyroidism in any cat in heart failure that is hyperthyroid.

Acromegaly

Acromegaly (hypersomatotropism) due to a pituitary somatotrophic adenoma is a rare cause of LV concentric hypertrophy in cats. In one study of 21 cats with acromegaly (all cats in this study also had diabetes mellitus), LV wall thickness ranged from 4 to 10 mm (ie, from normal to markedly thick).⁸⁹ This means that some cats with acromegaly have a normal heart while some have a severe HCM phenotype. As with hyperthyroidism, most likely the cats with severe LV wall thickening started with mild to moderate HCM, which was exacerbated by the acromegaly. Like hyperthyroidism, successful treatment often results in a decrease in LV wall thickness.⁸⁹ LA size may decrease also.

More recently, a group of cats with echocardiographic evidence of HCM was retrospectively screened for an elevation in circulating insulin-like growth factor 1 (IGF-1) concentration, which was assumed to be due to acromegaly.⁹⁰ A small percentage (7%) of the

It is imperative to control hyperthyroidism in any cat in heart failure that is hyperthyroid.



60 cats examined had an elevation in IGF-1. None of these four cats had diabetes mellitus. Therefore, it is possible that some cats diagnosed with HCM and without diabetes mellitus may have acromegaly. However, none of these cats had a CT or MRI scan or necropsy performed to prove whether or not they actually had a pituitary adenoma.

Supplementary material

Brief outlines of the supplementary files are provided below; fuller descriptions accompany the files that are available online at journals.sagepub.com/doi/suppl/10.1177/1098612X211030218.

- ❖ Files 1–3: Videos showing echocardiography, including color flow Doppler in file 3, of a cat with DCM.
- ❖ Files 4–6: Videos showing echocardiography of a cat with the endomyocardial form of RCM. *Courtesy of Seunggon Lee, DVM.*
- ❖ File 7: Video of the ultrasonographic view of the liver of a cat with ascites and an enlarged hepatic vein due to right heart failure.
- ❖ Files 8 and 9: Videos showing the echocardiographic view of a cat with ARVC. *Courtesy of Ashley N Sharpe, DVM.*
- ❖ Files 10–14: Videos showing echocardiography, including color flow Doppler in file 12, of a Maine Coon cat with LVNC.
- ❖ Files 15–18: Videos showing echocardiography, including color flow Doppler in file 18, of a cat with NCM.

Conflict of interest

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Ethical approval

This work did not involve the use of animals and therefore ethical approval was not specifically required for publication in *JFMS*.

Informed consent

This work did not involve the use of animals (including cadavers) and therefore informed consent was not required. No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

KEY POINTS

- ❖ Although DCM in cats due to taurine deficiency is rare, it can still occur with diets that are not commercially manufactured.
- ❖ RCM encompasses several distinct forms. The definitive diagnosis relies on identifying an abnormal pattern of LV filling using spectral or tissue Doppler echocardiography.
- ❖ RV dilation together with tricuspid regurgitation and ventricular arrhythmias can present a diagnostic dilemma – is it TVD or ARVC? However, treatment is usually the same.
- ❖ LVNC is likely an underrecognized entity in cats.
- ❖ The diagnosis of NCM should always be accompanied by a complete description of the abnormalities noted echocardiographically.



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