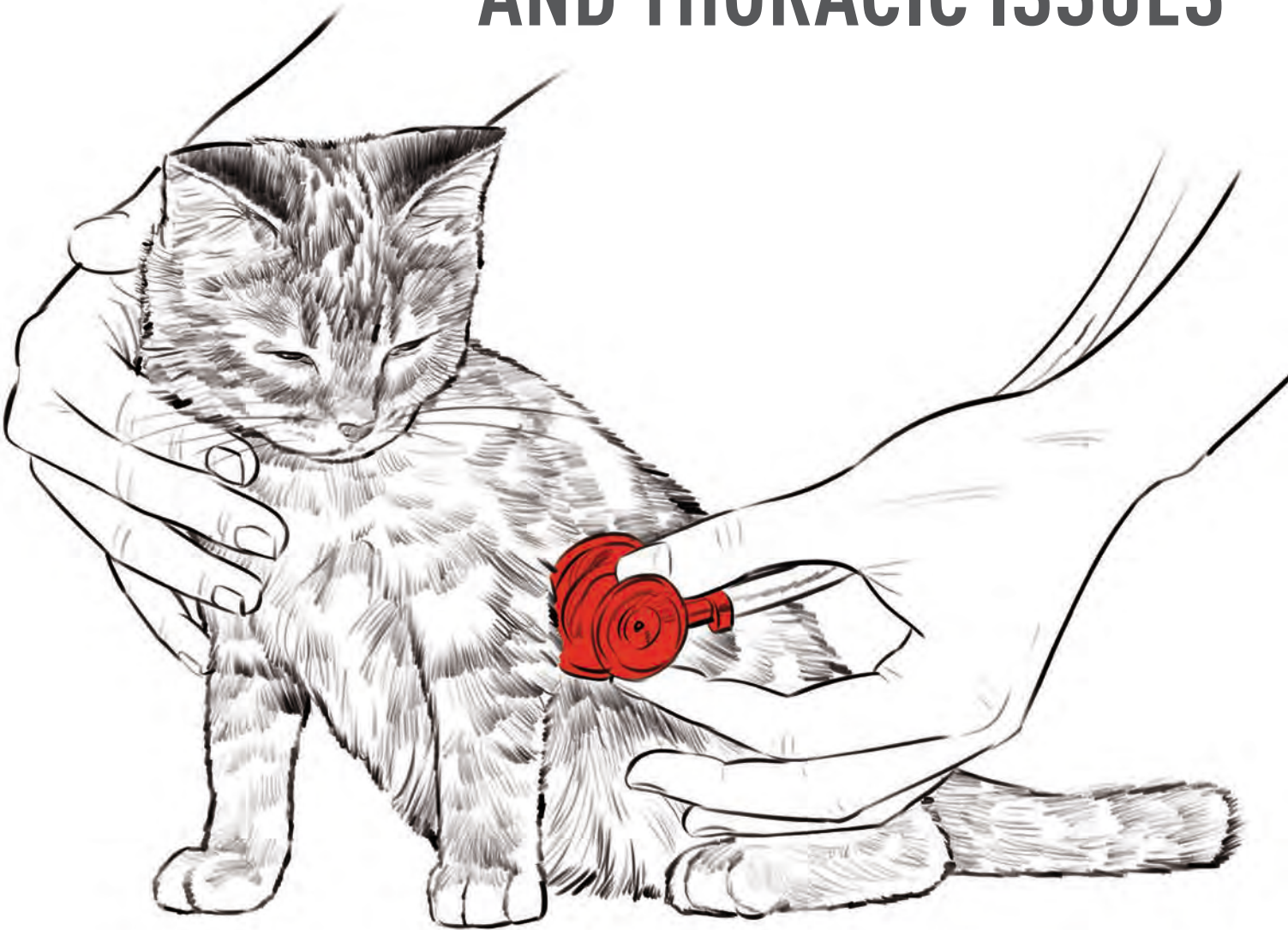


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FELINE CARDIAC AND THORACIC ISSUES



Pre-clinical feline hypertrophic cardiomyopathy – Cardiac biomarkers in the cat – Syncope in the cat – Management of the cat with heart failure – Feline systemic hypertension – Feline mediastinal lymphoma


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猫に小判 (Neko ni koban)

"Do not throw your pearls before swine, or they will trample them underfoot." – Matthew 7:6

The above phrase may not be recognizable unless you are fluent in Japanese, but it translates literally as "gold coins to a cat" – which may not leave you much the wiser, unless you know that whilst the Japanese, like many cultures, often use proverbs, they will frequently cite only the first part of a common phrase for brevity. So, whereas we might say "killing two birds with one stone", they would reduce this to something like "one stone two birds". Hence "gold coins to a cat" is comparable to the Biblical saying "cast not pearls before swine" – or in other words, do not give something of value to someone who does not appreciate it.

A more common link between the feline species and Japan is the *maneki-neko* (招き猫), which translates as the "beckoning cat". This takes the form of a small statuette which is believed to bring good luck to the owner; most of us will have come across one of these "lucky cats", perhaps sitting in the window of an oriental restaurant, shop, bar or other business. Although they vary in color, style and detail, they are unmistakable in that they traditionally portray a cat sitting upright, with a raised forepaw. Sometimes the figurine will encompass a mechanical device that makes the paw move slowly up and down, which mimics the oriental beckoning gesture – the idea being that it encourages people to enter the establishment. In fact, the talisman extends beyond business; modern Japanese superstition suggests that keeping a *maneki-neko* in bedrooms and places of study will bring about favorable results and success in life.

Which serves as an introduction to this issue of *Veterinary Focus*. The subject is feline thoracic



Ewan McNEILL
Editor-in-chief

medicine, and the table of contents beckons the reader to discover what lies within. There is, however, no need for a specious mascot in order to profit from the journal, and there is no danger of gold coins being thrown to a cat here; readers will surely appreciate and benefit from the pearls of knowledge being offered by our authors.

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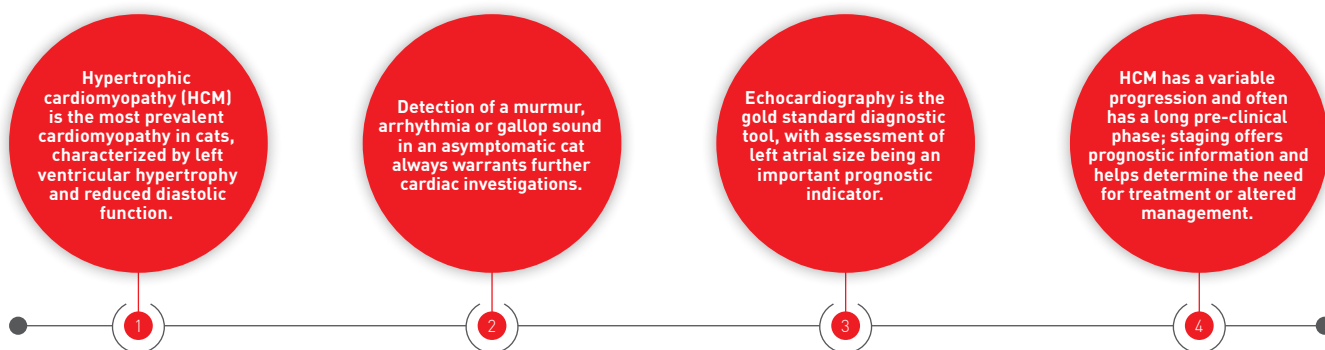
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PRE-CLINICAL FELINE HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is prevalent in the pet cat population, but affected animals may not be easy to identify; this paper offers a comprehensive overview of the condition for the first-opinion veterinarian.

KEY POINTS



Introduction

Feline hypertrophic cardiomyopathy (HCM) is a primary myocardial disease defined by left ventricular (LV) concentric hypertrophy, *i.e.*, thickening of the LV walls [1]. It is a disease of diastolic dysfunction (impaired relaxation), normally with preserved systolic function (contractility). The reduced compliance of the myocardium affects the ability of the heart to relax and fill during diastole, with consequent increased diastolic pressure, resulting in progressive left atrial (LA) dilation [2]. HCM is a diagnosis of exclusion, with the need to rule out other possible cardiac or systemic diseases which may be causing or contributing to a HCM phenotype, such as systemic hypertension, hyperthyroidism, acromegaly and aortic stenosis. The disease progression is highly variable, and often has a prolonged asymptomatic, pre-clinical phase which frequently goes undetected. Cats may subsequently present with signs of congestive heart failure (CHF), arterial thromboembolism (TE) or arrhythmias [2,3].

Prevalence and signalment

HCM is the most common feline cardiomyopathy, estimated to affect 14.5-34% of the "healthy" cat population [1,4]. Domestic short- and longhair cats account for most cases [4], but pedigree breeds with a predilection for HCM include Persians, British Shorthair, Maine Coon, Ragdoll, Sphynx, Himalayan and Bengal. Any age may be affected, but purebred cats in particular may present with severe disease at a young age [4]. HCM is over-represented in male cats, accounting for 75% of cases, despite no sex-linked heritable pattern being identified.

Etiology

Familial HCM in Maine Coon, Ragdoll and Sphynx cats [5-7] is a result of mutations in sarcomeric proteins, but in all other cats the cause remains unknown, although it is likely heritable in other purebreds. The sarcomere is the contractile component of cardiomyocytes, with mutations to sarcomeric proteins resulting in altered sarcomere structure and function which ultimately lead to impaired cardiomyocyte performance. The exact



Joanna Dukes-McEwan

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Professor Dukes-McEwan graduated in 1986 from the University of Glasgow and remained there to do an internship and residency training. After a spell in general practice, she moved to Edinburgh Veterinary School as a lecturer and researcher, which resulted in her PhD in familial dilated cardiomyopathy in Newfoundland dogs. A Diplomate of the ECVIM, Professor Dukes-McEwan has been based at the University of Liverpool since 2004, where she is responsible for undergraduate cardiology teaching as well as being involved in clinical research, having authored or co-authored over 80 publications. She is the current chair of the cardiology specialty for ECVIM-CA and serves on their executive board, and was awarded Fellowship of the Royal College of Veterinary Surgeons in 2017 for meritorious contributions to clinical practice.



Catheryn Partington

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Dr. Partington graduated from the University of Liverpool in 2014, having also attained a Masters in Veterinary Science, and returned to the University for both her rotating internship and cardiology residency, completing the latter in 2021. She has also worked in first opinion and emergency practice and is now studying towards ECVIM-CA cardiology Diplomate status. She has a passion for feline cardiomyopathies and was recently appointed clinical cardiologist at the University of Cambridge, where she also finds time for clinical research and teaching.

process by which sarcomere dysregulation leads to the HCM phenotype is complex and not fully understood. Changes in calcium sensitivity, mechanical function and cell stress culminate in myocyte hypertrophy, collagen synthesis and myocyte disarray – the histopathological hallmarks of feline HCM [4,8].

Two different mutations to the myosin binding protein C in the sarcomere have been identified in Maine Coons and Ragdolls (A31P and R820W respectively) [5,6]. Individuals heterozygous for the mutation often have subclinical disease, with changes only at a cellular, not gross, level, but homozygote cats are more severely affected; an incomplete dominance mode of inheritance is suspected. Maine Coons without the mutation can still develop a HCM phenotype, reflecting the likely multifactorial etiology of the condition. More recently a mutation in the ALMS1¹ gene has been identified as a causative factor for HCM in Sphynx cats [7].

further reducing myocardial compliance (*i.e.*, increased stiffness). Consequently, the diastolic pressure within the LV for any given volume of blood increases, in turn increasing pressure within the LA, which then enlarges. Elevated LA pressure is transmitted back to the pulmonary veins, and when pulmonary venous pressure exceeds 25 mmHg, pulmonary edema, the characteristic feature of left-sided CHF, ensues [4]. In cats the veins draining the lung pleura open into the pulmonary veins, allowing pleural effusion to develop with left-sided CHF (differing to dogs, in which pleural effusion is always a result of right-sided CHF, never left-sided) [4].

Progressive LA enlargement is one of the factors predisposing cats with severe HCM to thromboembolic disease, although this condition is outwith the scope of this article. The marked hypertrophy, reduced oxygen supply and replacement fibrosis within the myocardium act as substrates for the development of arrhythmias.

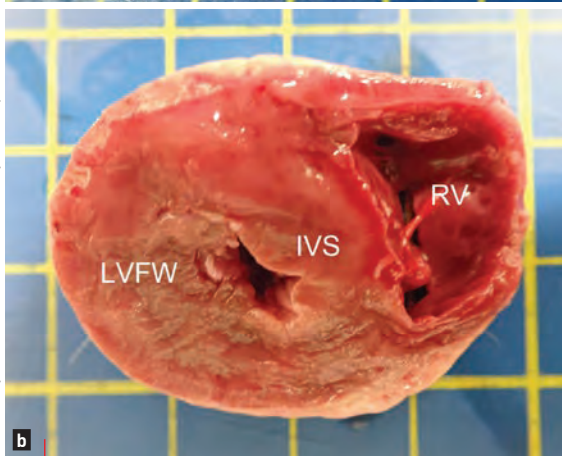
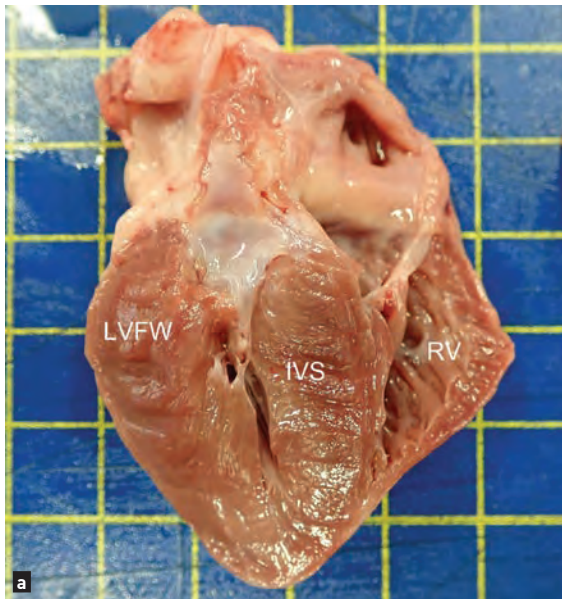
LV hypertrophy in feline HCM may affect both the interventricular septum and free wall, or the changes can be asymmetric, with only a focal region affected – typically the base of the interventricular septum. Hypertrophy may also affect the right ventricle, but the pattern and distribution can be highly variable between individuals (**Figures 1 and 2**) [4]. There may also be changes to the mitral valve apparatus, including elongation of the anterior mitral valve leaflet and papillary muscle hypertrophy. Systolic anterior motion (SAM) of the mitral



Pathophysiology

As noted above, HCM manifests as LV hypertrophy and diastolic dysfunction, whereby pathological changes reduce the ventricle's ability to relax and fill during diastole. Furthermore, progressive hypertrophy of the wall reduces blood supply to the cardiomyocytes, which are replaced by fibrous tissue as they die,

¹ ALMS: Alstrom syndrome 1



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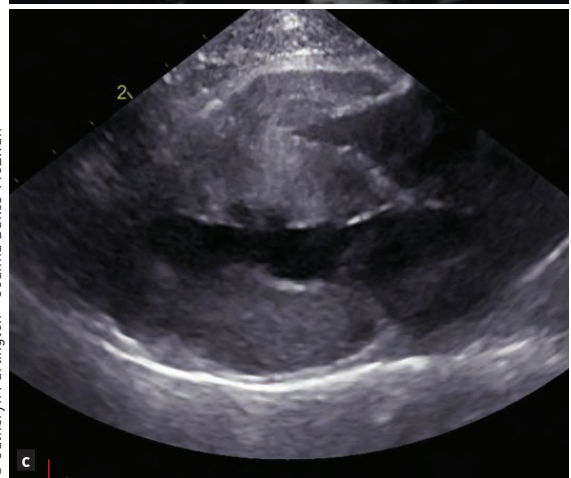
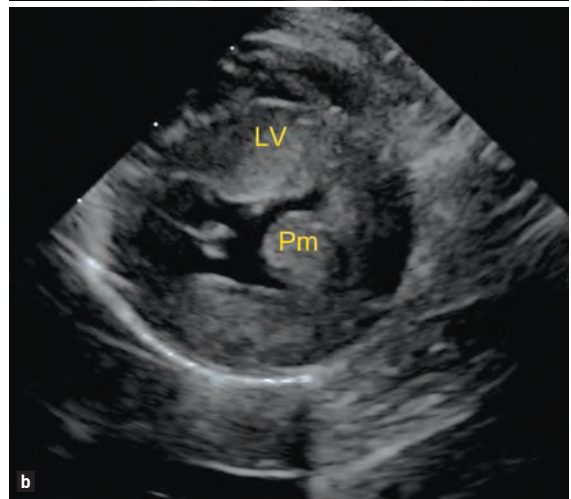
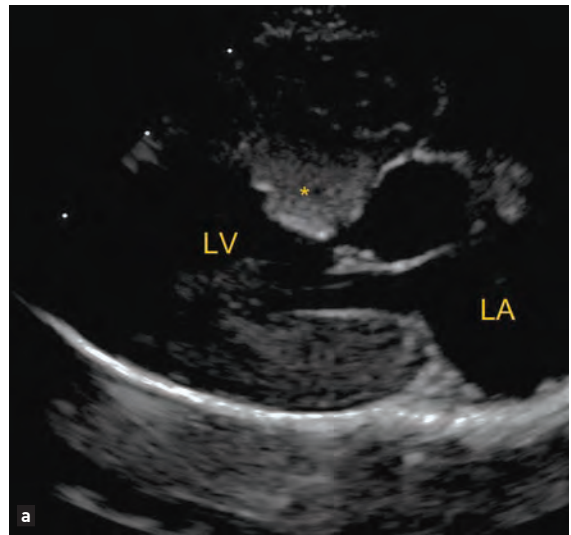
Figure 1. The pattern of LV hypertrophy in feline hypertrophic cardiomyopathy can be highly variable between individuals, but both these gross pathology specimens show diffuse left ventricular hypertrophy.

Abbreviations: LVFW; left ventricle free wall; IVS; interventricular septum; RV; right ventricle



“The reduced compliance of the myocardium reduces the ability of the heart to relax and fill during diastole, with consequent increases in diastolic pressures, resulting in progressive left atrial dilation.”

Catheryn Partington



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Figure 2. Echocardiographic views of HCM can show great variability. **(a)** A right parasternal long axis 5 chamber view showing a focal region of hypertrophy affecting the basal septum (*). **(b)** A right parasternal short axis view at the level of the papillary muscles showing left ventricular and papillary muscle hypertrophy. **(c)** A right parasternal long axis 4 chamber view showing symmetric hypertrophy of the interventricular septum and left ventricular free wall. **Abbreviations:** LA left atrium, LV left ventricle, Pm papillary muscle.

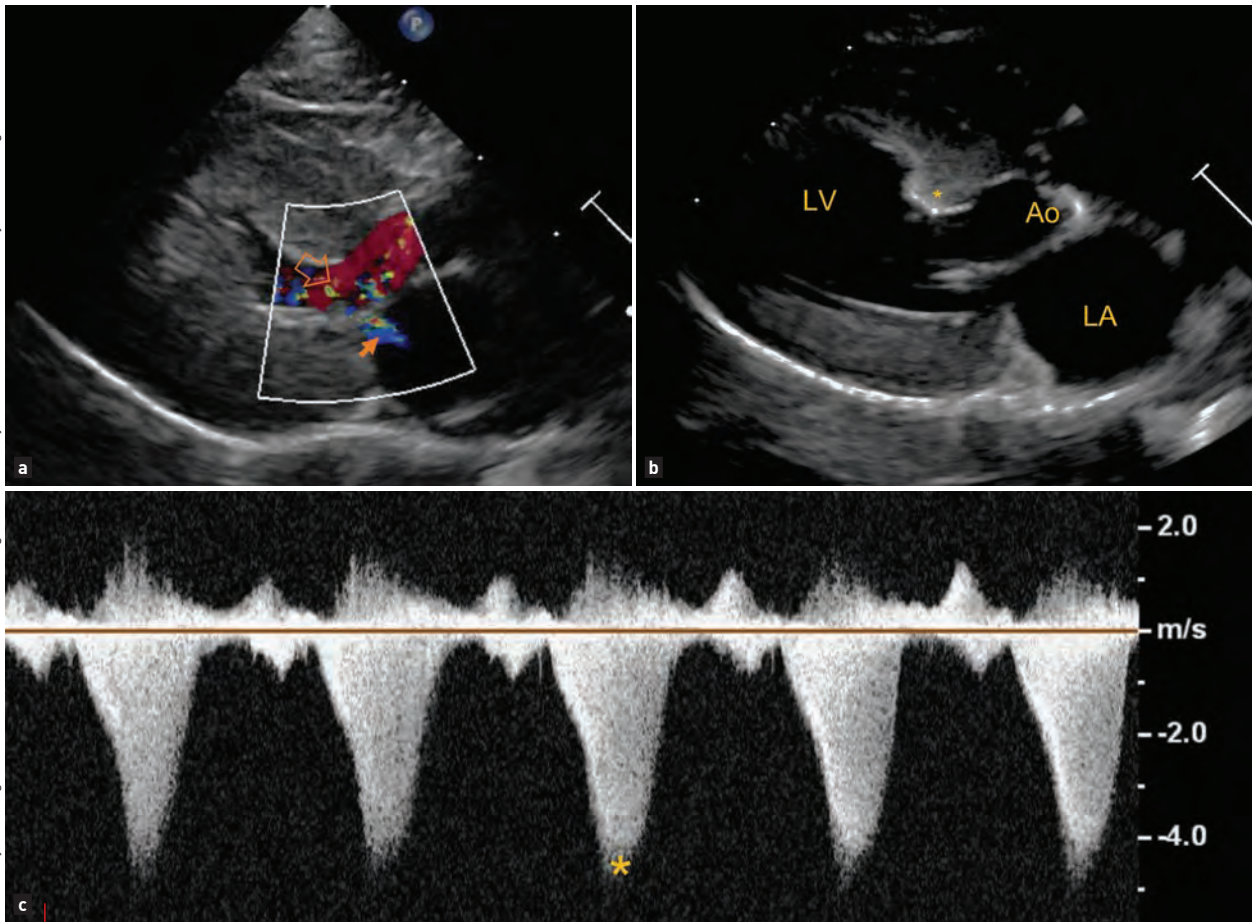


Figure 3. Murmurs in cats with HCM most often result from left ventricular outflow tract obstruction (LVOTO). **(a)** A right parasternal long axis 5 chamber view with color flow Doppler showing a turbulent jet of blood flow in the left ventricular outflow tract (open arrow) caused by systolic anterior motion of the mitral valve and a small eccentric jet of mitral regurgitation (small arrow). **(b)** A right parasternal long axis 5 chamber view showing focal basal septal hypertrophy (*) as a cause of LVOTO. **(c)** Spectral Doppler of the LVOT showing increased velocities (*) and biphasic acceleration (classic “scimitar” shape), indicative of LVOTO. **Abbreviations:** Ao aorta, LA left atrium, LV left ventricle.

valve is a common feature of HCM and may cause significant left ventricular outflow tract obstruction (LVOTO) [9,10].

Left ventricular outflow tract obstruction

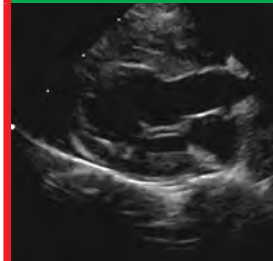

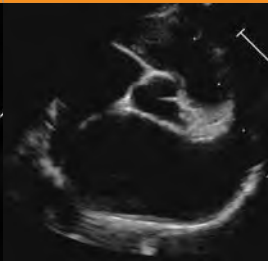


A subset of cats with HCM may have significant LVOTO (**Figure 3**). Such cases have classically been termed hypertrophic obstructive cardiomyopathy (HOCM), but human medicine has moved away from this term, as the presence of LVOTO can be intermittent, and as the same is true for cats, the term is likely outdated [3,9,11]. LVOTO may be a result of SAM of the mitral valve, focal hypertrophy of the basal septum, or, less commonly, mid-cavity obstruction due to papillary muscle hypertrophy [4,9,12]. This LVOTO causes a murmur due to increased turbulence of blood. With SAM, the obstruction is typically dynamic, worsening with increased cardiac contractility, such as during physical or emotional stress. This is often the reason for variability in the presence or intensity of murmurs in cats with HCM.

SAM of the mitral valve occurs when the septal (anterior) leaflet (often elongated) is pulled towards the outflow tract as a result of hypertrophy and displacement of the papillary muscle, which cause slack chordae tendineae [10]. As the outflow tract becomes narrowed by this abnormal movement of the leaflet (or by basal septal hypertrophy), the blood velocity increases and the pressure decreases, dragging the tip of the leaflet further into the outflow tract and worsening the obstruction (the Venturi effect) [4,9]. SAM is thought to increase myocardial oxygen demand and reduce coronary perfusion, increasing the risk of myocardial ischemia; it is likely associated with progressive hypertrophy and microvascular dysfunction. It is thought that some cats with severe LVOTO show signs of reduced exercise capacity and angina-type pain, as described in people.

Transient myocardial thickening

Transient myocardial thickening (TMT) is an important differential diagnosis for a HCM phenotype. It is uncommon and poorly understood, but is characterized by increases in LV wall

Box 1. ACVIM staging of feline HCM.

<p>Stage A: cats predisposed to, but with no current evidence of, HCM; e.g., a Maine Coon with the A31P gene mutation, or a cat with a close relative diagnosed with HCM. The heart will be structurally normal on ultrasound scan.</p>	<p>Stage B: cats with preclinical HCM (i.e., no clinical signs but echocardiographic evidence of HCM). This is further subdivided based on disease severity and risk of CHF and TE.</p> <p>Stage B1: low risk of developing CHF or TE, with a normal or mildly dilated LA.</p> <p>Stage B2: higher risk of imminent CHF or TE, with moderate to severe dilation of the LA.</p>		<p>Stage C: cats with clinical signs of HCM and CHF or TE.</p>	<p>Stage D: HCM cats with CHF refractory to treatment.</p>
<p>Stage A</p>	<p>Stage B1</p>	<p>Stage B2</p>	<p>Stage C</p>	<p>Stage D</p>
				

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thickness and LA dilation which are less marked than that seen in primary HCM, and there is full resolution of clinical signs and echocardiographic changes over a period of some months. TMT is thus associated with an excellent prognosis. Cats presenting with CHF secondary to TMT tend to be younger than those with primary HCM, and an antecedent event (such as general anesthesia) is often reported. It has been postulated that increased wall thickness is due to myocardial edema, with similarities to both acute myocarditis and stress-induced cardiomyopathy in humans (13).

severe LA dilation, reduced LA systolic function, spontaneous echo contrast, severe wall hypertrophy (>9 mm), LV systolic dysfunction and focal wall thinning are associated with an increased risk of CHF and/or TE (2,15).

●●● Staging and prognosis of HCM

The recent ACVIM guidelines on the diagnosis and treatment of HCM (14) outline a staging system, similar to that used for myxomatous mitral valve disease in dogs (Box 1). This system can help determine whether treatment is indicated, as well as provide owners with some expectation of what lies ahead – as the progression of HCM, and thus prognosis, is highly variable. In some cats the disease is progressive, leading to CHF, TE and cardiac death, while others may remain pre-clinical and eventually die from non-cardiac causes (14,15). The reason for such heterogeneity remains unclear, and it is difficult to predict which cats may succumb to their disease, although several retrospective studies have identified a number of prognostic factors. Cats diagnosed at a younger age tend to have longer survivals (2). Cats which develop CHF secondary to factors such as stress or intravenous fluid therapy (IVFT) typically have longer survival than other stage C HCM cats. The presence of gallop sounds, arrhythmias,

●●● Why identify pre-clinical cats?

Due to the reduced diastolic function and subsequent increase in pressures for any given volume of blood within the LV, cats with HCM are more sensitive to increases in circulating volume (i.e., increased preload). Certain treatments, such as prolonged corticosteroid use and IVFT, could therefore push a cat with advanced HCM into left-sided CHF. This highlights the importance of identifying cats with pre-clinical disease, so that such treatments can be modified and closely monitored (e.g., lower IVFT rates, closer monitoring of respiratory rates, and sequential imaging to assess left atrial size) to reduce risk of decompensation. Furthermore, cats with advanced HCM are at risk of thromboembolism, and identifying these individuals allows initiation of preventative antiplatelet therapy.

Identification of stage B cats may facilitate detection of subtle signs of early progression to stage C, as owners may be better educated and more vigilant regarding the signs of CHF, thus allowing initiation of treatment before there is fulminant pulmonary edema and severe respiratory compromise.



How to diagnose the asymptomatic cat

The challenge with HCM is the variable length of the pre-clinical phase, and the frequent lack of any clinical signs or alterations on physical examination. Changes on clinical exam which would raise suspicion of stage B HCM include the presence of a murmur (**Box 2**), gallop sounds (**Box 3**) or arrhythmia [4]. While many asymptomatic cats with HCM will present with a murmur, upwards of 31-62% will not have a murmur; furthermore, 25-33% of cats with left parasternal systolic murmurs (typically soft, low-grade) have no echocardiographic evidence of a cardiomyopathy [1,4]. Louder murmurs (> grade 3/6) are more likely to be associated with significant cardiac disease [4], but any murmur warrants further investigation.

Echocardiography

Echocardiography is the gold standard for diagnosis of HCM [14], and if hypertrophy is identified, causes of secondary hypertrophy should be investigated [see article on page 26]. Echocardiography should be advised for any cat with clinical signs possibly attributable to a cardiomyopathy (syncope, exercise intolerance, intolerance to IVFT), those with a familial history of HCM (or sudden death), pedigree cats intended for breeding, and cats where physical exam findings are suggestive of a cardiomyopathy (gallop sounds, arrhythmias, murmur, tachypnea, dyspnea, reduced lung sounds). The ACVIM consensus also advises that cats over 9 years of age undergoing interventions that may precipitate CHF (e.g., general anesthesia, IVFT and prolonged corticosteroid therapy) should also undergo echocardiographic assessment [14].

For the asymptomatic cat, there are four major criteria assessed on echocardiography: LV wall thickness, LA size, presence of LVOTO, and diastolic



“The challenge with HCM is the variable length of the pre-clinical phase, and the frequent lack of any clinical signs or alterations on physical examination.”

Joanna Dukes-McEwan

Box 2. Causes of murmurs in pre-clinical HCM.

Murmurs are heard when blood flow becomes turbulent; this can be due to high velocity blood flow, large diameter vessels, high fluid density or low viscosity. In HCM murmurs are most often a result of left ventricular outflow tract (LVOT) obstruction due to systolic anterior motion of the mitral valve and/or focal basal septal hypertrophy.

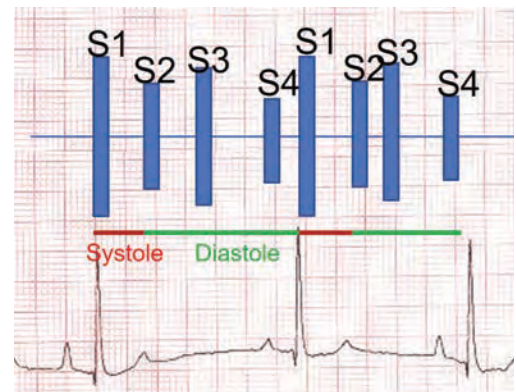
- Systolic anterior motion (SAM) of the mitral valve; abnormal movement of the anterior leaflet of the mitral valve into the left ventricular outflow tract creates a dynamic obstruction to blood flow, with increased velocity of blood past the obstruction. With SAM the mitral valve also becomes incompetent, resulting in mild mitral regurgitation, which may also be heard as a murmur (**Figure 3a**).
- Focal basal septal hypertrophy; hypertrophy of the left ventricle may be focal and often occurs isolated to the base of the interventricular septum. This is seen as a region of wall appearing to bulge into the LVOT, causing obstruction (**Figure 3b**).

Murmurs in cats with HCM are often dynamic, meaning they may change in intensity, and may even at times be absent. The degree of obstruction is likely worse when the heart contracts with more force (i.e., with increased catecholamines from stress), creating a louder murmur.

Box 3. What are gallop sounds?

In most healthy cats and dogs only the first (S1) and second (S2) heart sounds are detected on auscultation. A gallop sound is an audible additional heart sound, creating a three-beat cadence, similar to the footfalls of a galloping horse.

This may be due to either an audible third (S3) or fourth (S4) heart sound, although it is often difficult to differentiate between these on auscultation. S3 is a result of rapid ventricular filling in early diastole, whilst S4 is a result of active ventricular filling via atrial contraction in late diastole.



Auscultation of gallop sounds is generally indicative of the presence of diastolic dysfunction, with 2.6-19% of cats with subclinical HCM having a gallop sound [19]. They are rarely auscultated in healthy cats, so detection should always prompt further cardiac investigations.

function. The first two are relatively easily assessed by a general practitioner with basic echo competency in cases with moderate to severe disease.

1) Left ventricular wall thickness

Both the interventricular septum and LV free wall should be assessed, with measurements made on 2-dimensional echocardiography, on right parasternal views at end-diastole (the frame prior to closure of the mitral valve leaflets) (**Figure 4a**). As hypertrophy can be focal, measurements should be taken over at least three cardiac cycles and ideally from multiple locations. Care should be taken not to include papillary muscles or regions of marked endocardial thickening in wall measurements. An end-diastolic LV wall thickness less than 5 mm is normal, while ≥ 6 mm is consistent with hypertrophy (14). Values of 5-6 mm remain a gray area and should be considered with respect to body size, breed and other echocardiographic variables (16).

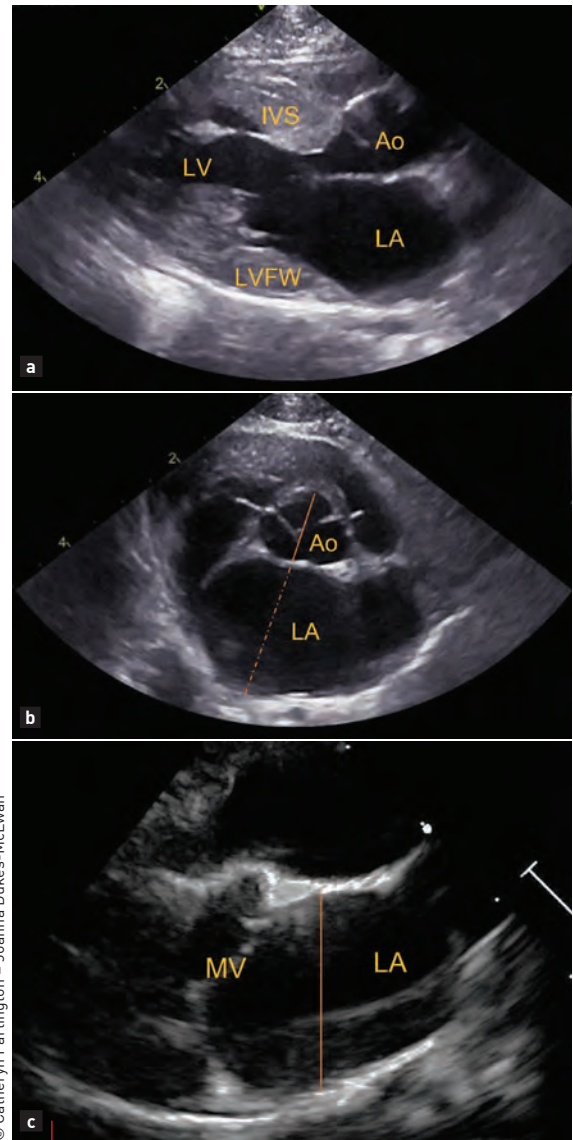
2) Left atrial size

LA size is an independent risk factor for CHF, TE and cardiac death, and can be assessed on both right parasternal long and short axis views. On short axis views at the level of the heart base, measurements are made at early diastole (the frame after closure of the aortic valve cusps), with the atrial diameter being indexed to the aorta (LA/Ao; **Figure 4b**). The aorta is measured from the midpoint of the convex curvature of the wall of the right aortic sinus to the point where the aortic wall, non-coronary and left coronary aortic cusps merge. The LA is measured from this latter point to the LA free wall, avoiding entering the pulmonary vein (17).

On the right parasternal long axis four chamber view the LA should be optimized and the left atrial diameter (LAD) measured at end systole (the frame prior to mitral valve leaflet opening), drawing a line parallel to the mitral annulus from the interatrial septum to the LA free wall (**Figure 4c**) (18). An LA/Ao > 1.6 and LAD > 16.0 mm is consistent with LA enlargement; an LA/Ao $> 1.8-2.0$ or LAD $> 18-19$ mm is considered moderate to severe LA enlargement. LA fractional shortening can also be evaluated to assess systolic function. Subjective assessment of the left auricular appendage size, presence of spontaneous echo-contrast or a thrombus, and assessment of left auricular appendage velocities are also important in assessing CHF and TE risk.

3) Presence of LVOT obstruction

This can be assessed on 2-dimensional, M-mode, color flow and spectral Doppler (**Figure 3c**). SAM can be visualized on both 2-dimensional and M-mode. Color flow Doppler will highlight turbulence in the LVOT and possibly mitral regurgitation. Spectral Doppler to assess LVOT velocities requires good alignment to flow; with dynamic obstruction the Doppler profile will often show biphasic acceleration (a classic scimitar shape).



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Figure 4. Echocardiographic assessment of hypertrophic cardiomyopathy (HCM). **(a)** A right parasternal long axis 5 chamber view. The left ventricular free wall and interventricular septal thickness should be measured on 2 dimensional images in diastole; values ≥ 6 mm are consistent with hypertrophy. **(b)** A right parasternal short axis view at the level of the heart base. The left atrial size is indexed to the aortic root (LA/Ao), measured in early diastole; values > 1.6 are consistent with left atrial dilation. **(c)** A right parasternal long axis 4 chamber view. The left atrium diameter is measured parallel to the mitral annulus at end systole; values > 16.0 mm are consistent with left atrial dilation.

Abbreviations: Ao aorta, IVS Interventricular septum, LA left atrium, LV left ventricle, LVFW left ventricular free wall, MV mitral valve.

4) Diastolic function

Diastolic function can be assessed by both spectral Doppler and Tissue Doppler imaging, but further discussion is beyond the scope of this article. Cats with advanced HCM may also have impaired systolic function.



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Figure 5. Clinicians in first-opinion practice should be alert for signs of HCM in their patients, and all feline examinations should involve careful cardiac auscultation for the presence of murmurs, gallop sounds and arrhythmias, any of which warrant further investigation. This is especially the case in breeds that are prone to cardiomyopathies, and tests are now available to detect the genetic mutation that can be responsible for HCM in the Sphynx cat.

Radiography

Thoracic radiography is the gold standard for diagnosis of pulmonary edema, but is less useful in asymptomatic cats [14]. Severe cardiomegaly with LA bulging may be seen, however radiographs have a lower sensitivity for detection of mild to moderate remodeling in HCM patients, many of which may have a normal cardiac silhouette.

Cardiac biomarkers

Biomarkers will be discussed in greater detail elsewhere, but in brief these can be a useful tool when used in adjunct to other diagnostics and for monitoring of disease progression, although they should be used with caution as a screening tool. For the asymptomatic cat, quantitative NT-proBNP (a marker of myocardial stress and stretch) has limited use as a screening tool in the general population, as although it has high specificity, the sensitivity is low, meaning a high risk of false negative results. The test is likely better when used selectively in cases of suspected cardiomyopathy (*i.e.*, where a murmur is detected) [19] and along with echocardiography to gain a better understanding of the cardiomyopathy severity. The point-of-care (benchtop) NT-proBNP test is of more use in the symptomatic cat to discriminate between cardiac and non-cardiac causes of dyspnea [20].

Cardiac troponin I (Tn I), a marker of cardiomyocyte injury, is again useful alongside echocardiography, and has been shown to have prognostic significance, with increased values associated with poorer outcomes [21]. Myocardial ischemia may result in high levels, which is reported in advanced feline HCM. Severe

elevations may raise suspicion of myocarditis causing a secondary HCM phenotype, warranting further investigations.

Both biomarkers have been shown to be higher in cats with HCM and SAM, than in HCM cases without SAM, even in cats with normal/equivocal LA size [22].

Genetic testing

Genetic testing is available for Maine Coon, Ragdoll and Sphynx cats (**Figure 5**), and is recommended in all breeding cats of these breeds to reduce the inheritable prevalence of HCM. It is advised that individuals homozygous for the mutation are not bred, while heterozygotes may be bred with individuals negative for the mutation [14]. It is, however, important that breeders are aware that cats without the known genetic mutations may still develop HCM.

●●●● Treatment

Staging of cats with HCM can help standardize treatment. No treatment is indicated for stage A and stage B1 (no/minimal left atrial dilation) cats, except in cases of severe LVOTO, in which beta-blockers may be considered (see below). Stage B2 cats are at risk of TE, and clopidogrel as a preventative therapy is advised. Treatment of cats in stage C and D will be discussed in the article on page 26.

As in human HCM, insulin, insulin-like growth factor-1 and inflammation have been shown to likely be implicated in the pathophysiology of



CONCLUSION

Given that HCM has high prevalence in cats, with a tendency for a long pre-clinical phase and risk of serious clinical signs, the general practitioner should be alert for signs of stage B disease in their feline patients. All examinations should include careful auscultation for the presence of murmurs, gallop sounds and arrhythmias, any of which would warrant further investigation. Detection of stage B cats allows initiation of preventive therapy where applicable, as well as risk management prior to interventions or treatments which could precipitate decompensation. Improved owner education and vigilance may also facilitate detection of congestive heart failure prior to the development of severe respiratory compromise.

feline HCM. Diet alterations targeting these factors may therefore have beneficial effects; one recent study showed that cats with pre-clinical HCM fed a diet restricted in starch and supplemented with omega-3 fatty acids had reduced LV remodeling. The advent of a commercially available feline cardiac diet now offers the veterinarian the option to choose this as a therapeutic intervention in stage B cats [23].

In people with HCM and severe LVOTO, exercise intolerance and angina are commonly reported; with improvement of clinical signs following beta blocker therapy. Their use in pre-clinical cats with evidence of LVOTO remains debatable, and the authors advise that cases are referred to a cardiologist for this decision to be made. Theoretically, beta blockers would appear favorable in cases of marked LVOTO; the negative inotropic and chronotropic effects may reduce the severity of obstruction, while also improving myocardial oxygen supply, reducing risk of arrhythmias and ischemia. However, no benefit to long-term survival nor to quality of life has been proven [24,25]. Furthermore, beta blockers are contraindicated in cases of CHF and would likely be detrimental to cats close to decompensation.



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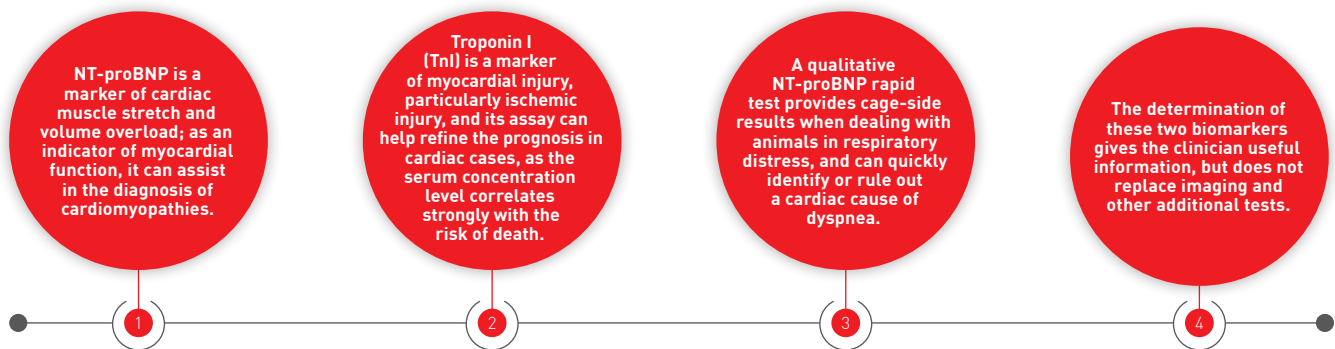
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CARDIAC BIOMARKERS IN THE CAT

Recent advances have identified biomarkers that can aid in the diagnosis of feline heart disease; this paper discusses the uses – and limitations – of these tests.

KEY POINTS



Introduction

NT-proBNP and troponin I are frequently cited in feline medicine as part of the panel of complementary examinations used by clinicians to investigate cardiac function or to search for possible myocardial lesions. With assay of these two biomarkers now widely available, this raises various questions, including:

- When should they be measured?
- Which one(s) should be chosen and why?
- How do they relate to other examinations such as thoracic imaging?
- How are the assay results interpreted?

Cardiac biomarkers

A biomarker is a substance which is assayed as part of the diagnostic procedure for specific conditions – in this case cardiac conditions. The ideal biomarker contributes to the screening, diagnosis, prognosis, and follow-up of different cardiomyopathies (1), and the assay should permit excellent sensitivity (*i.e.*, minimal false negatives) to allow early detection of disease, as well as good specificity (*i.e.*, minimal false positives) in order to maximize its reliability (2).

Troponin I

Troponins are proteins involved in the contraction and relaxation of cardiac and skeletal muscle. They are located in the myofibrils, along with actin and myosin, and exist in different isoforms (I, T, C) depending on the muscle in question (**Figure 1**).

Troponin I (TnI) is only present in heart muscle, which gives it 100% specificity, and is regarded as a marker of ischemic myocardial injury. Plasma concentrations of TnI increase in the hours following a cardiac lesion, and peak on the first day, although values can remain high for a week afterwards (3,4).

NT-proBNP

Natriuretic Peptides (NPs) are a family of hormones that regulate intravascular volume and control blood pressure. They are secreted by cardiomyocytes in response to abnormal cardiomyocyte stretch and volume and/or pressure overload, and they are also produced by other tissues. Their main effect is to counteract the action of the renin-angiotensin-aldosterone system, which is hyperactive in heart disease and responsible for cardiac remodeling. As the name indicates, NPs cause natriuresis, and they also influence diuresis, vasodilation, diastole, and vascular permeability, and inhibit multiplication of smooth muscle cells.

Brain Natriuretic Peptide, or BNP, was first isolated from porcine brain, but it is also secreted by the heart ventricles. In pathological conditions its serum levels increase, and it is therefore considered a marker of cardiac function. BNP is initially secreted as a precursor molecule, which is cleaved by serum proteases to form C-BNP, the active form, and NT-proBNP, the inactive form. C-BNP has a very short half-life (90 seconds), hence the use of NT-proBNP, which has greater stability during sampling and storage (2), and a half-life of around 120 minutes.



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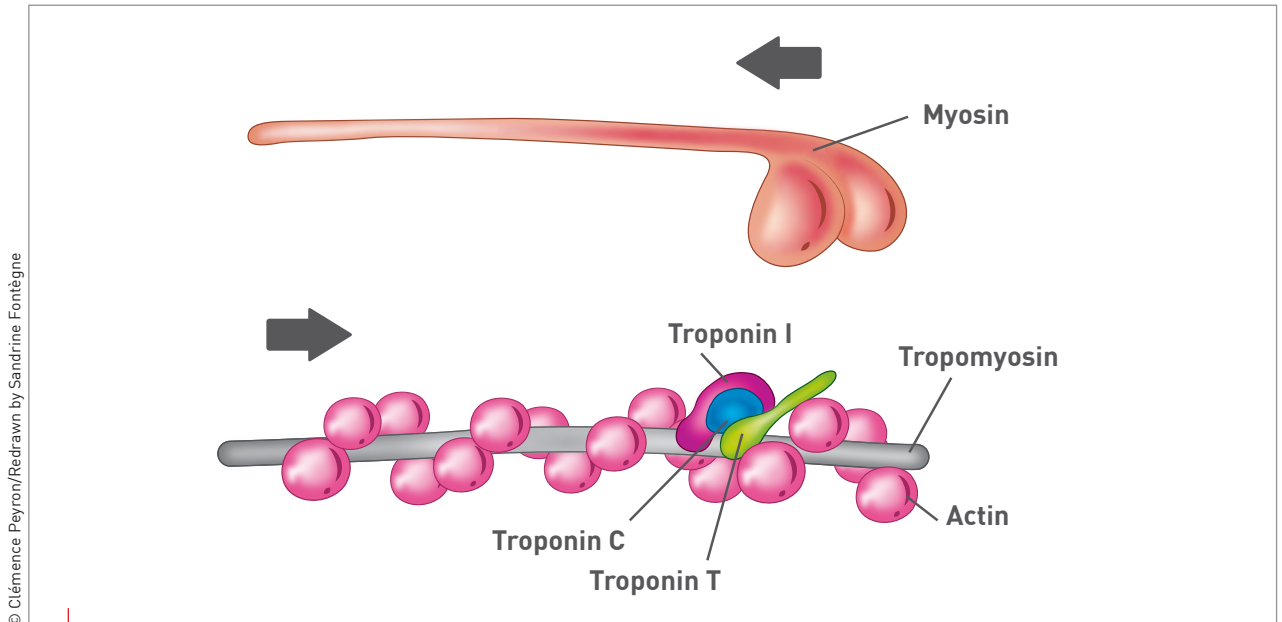


Figure 1. Conformation of the different proteins (actin, myosin, tropomyosin and troponins I, T and C), at the origin of the sliding movement of the filaments within the sarcomere in the cardiomyocyte.

●●● Biomarkers and feline cardiomyopathies

The term *cardiomyopathy* refers to a myocardial disorder characterized by one or more structural and/or functional abnormalities of the heart muscle, the most frequently described condition in cats being hypertrophic cardiomyopathy (HCM). This is the condition most often addressed in the literature and in studies that consider the role of biomarkers

in cardiac disease; to date, their role in other forms of cardiomyopathies, including restrictive, dilated and non-specific cardiomyopathies, have been studied in far less detail [5].

Investigation of cardiomyopathies requires various tests, some of which are specialist in nature (e.g., echocardiography and electrocardiography). Tests that can be performed in general practice include NT-proBNP, troponin I, chest radiographs and systemic blood pressure measurement.

Managing the patient and prioritizing the various complementary examinations will depend on the individual situation (e.g., a cat that simply requires screening for possible heart disease or the patient in respiratory distress). It is essential to recognize that NT-proBNP and Tnl assays sometimes have overlapping applications, and it is important to know what each one assesses in order to best target the diagnostic approach (**Table 1**).

Biomarkers for cats in respiratory distress

It is useful to quickly determine whether the cause of a cat's respiratory distress is of cardiac origin or not, and can avoid disturbing an often-unstable patient unnecessarily. The question of feasibility and the benefit/risk ratio must be considered (**Figure 2**) before taking blood samples. However, if radiography is inadvisable because the patient is unstable, a rapid (cage-side) NT-proBNP test like the SNAP® Feline proBNP test (**Figure 3**) may be considered, coupled (if possible) with a thoracic ultrasound scan. A negative result will suggest, with reasonable reliability, that the dyspnea is most probably non-cardiac in origin (5).

Studies in cats presented with respiratory distress and pleural effusion showed that the SNAP® Feline proBNP had a sensitivity of 93.9-100% and a specificity of 72.2-87.5% for diagnosing congestive heart failure as the cause of dyspnea using a blood sample (6-8). The test has also been performed using pleural effusion samples with very good sensitivity (*i.e.*, few false negatives) but variable specificity due to too many false positives (6). Another study showed better results when the pleural sample was diluted by half with 0.9% NaCl, giving a final sensitivity of 100% and a much better specificity of 85.7% (8). It should be noted, however, that the use of the cage-side SNAP® Feline proBNP is only officially validated on serum or EDTA plasma.

The main drawback of the quantitative NT-proBNP measurement assay is the time needed to send the sample to the laboratory and to obtain results, which can limit its use in an emergency situation. Nevertheless, it is a reliable test to differentiate between cardiac and non-cardiac respiratory distress (5). The various studies conducted report sensitivities of 86.4-100% and specificities ranging from 82.4-88.9% on blood samples. The sensitivities reported on undiluted pleural effusion are all 100% (no false negatives) with a specificity of 76.5-94.4%, depending on the threshold value used (7-9).

The Tnl assay can also help differentiate between a patient with cardiac respiratory distress and a patient with respiratory distress from other causes (**Figure 4**). In fact, cats with dyspnea resulting from a cardiomyopathy have significantly higher blood Tnl concentrations than healthy cats or cats where the dyspnea is not cardiac in origin (5,10). However, as with the quantitative NT-proBNP assay, this

analysis is usually performed in an external laboratory, which delays the results and can slow the diagnostic process, which can be problematic for patients requiring urgent care.

Biomarkers for suspected subclinical cardiomyopathy

Subclinical cardiomyopathy is defined as any form of cardiomyopathy that does not result in detectable clinical signs in the patient. It should be remembered that in some cases a cat may have an advanced cardiomyopathy before signs appear, and that affected cats can remain asymptomatic for a long time before suddenly deteriorating. In most cases the appearance of respiratory distress will prompt a consultation and subsequent investigations. However, in certain individuals at risk, or where auscultation may suggest an abnormality, early detection of a cardiomyopathy enables appropriate treatment which can delay the onset of decompensation. Therefore, non-invasive techniques that can be carried out in general practice are very useful, using biomarkers such as NT-proBNP or Tnl in the first instance.



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Figure 2. It may be essential to stabilize the feline cardiac patient before considering additional examinations, especially where there is respiratory distress; this can involve aspects such as minimal handling and use of an oxygen cage.

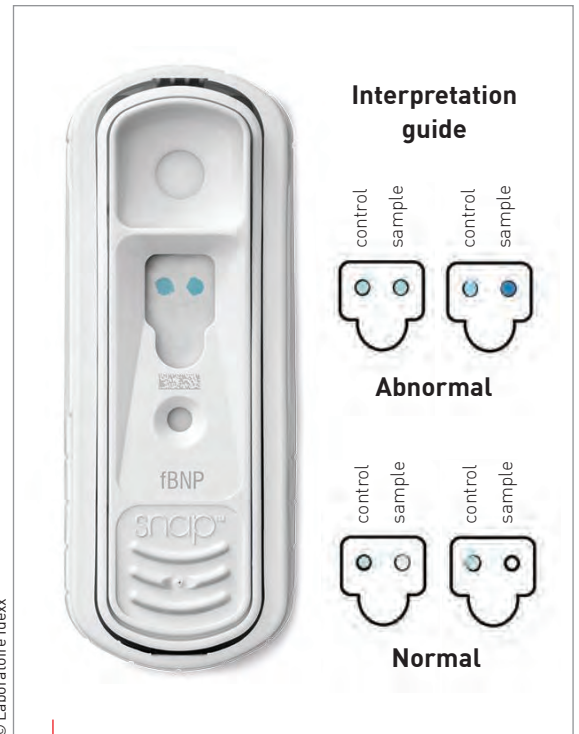
The rapid qualitative point-of-care tests are less useful in situations where the objective is a screen to determine if the patient can be considered healthy or as having subclinical cardiomyopathy. In a subclinical setting the main value of biomarker tests is to differentiate between cats with advanced cardiomyopathy and cats that are healthy or that have mild cardiomyopathy [5]. In one study of apparently healthy cats coming for screening, the SNAP® Feline proBNP showed a sensitivity of 43% (*i.e.*, many false negatives) and a specificity of 96% (few false positives). Sensitivity increased to 71%, with a specificity of 92%, when only asymptomatic cats with a heart murmur were included. These observations suggest that a positive SNAP® is likely to be associated with cardiomyopathy, warranting further investigation such as echocardiography, whereas a negative result does not exclude the presence of cardiomyopathy [11].

Quantitative NT-proBNP measurement is useful in investigating potential cardiomyopathy, especially when echocardiography is not available. However, this test is not recommended if the objective is to differentiate between a healthy cat and a cat with early stage HCM. Although plasma NT-proBNP concentration increases with the severity of cardiac injury, the overlap in values between different groups does not allow grading of cardiomyopathies (mild, moderate, severe) on the basis of NT-proBNP results alone [5]. In addition, a result that is within the usual reference interval is not sufficient to conclude that the patient is healthy, especially when early-stage cardiomyopathy is present, nor does such a result indicate that the patient will never develop cardiomyopathy. If there is a strong clinical suspicion of disease a “normal” result does not obviate the need for other complementary examinations, such as echocardiography. On the other hand, an abnormal result should always prompt further investigation [5]. However, one study showed that quantitative NT-proBNP measurement could distinguish cats with occult HCM from healthy cats and cats with obstructive vs.



“A negative SNAP® test will suggest, with reasonable reliability, that the dyspnea is most probably non-cardiac in origin.”

Clémence Peyron



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Figure 3. The SNAP® Feline proBNP uses an ELISA (enzyme-linked immunosorbent assay) technique to detect normal or abnormally raised levels of proBNP in serum or EDTA plasma. It includes a bidirectional flow method that improves sensitivity (as the sample gets two chances to bind to the antibodies) and a wash step to maximize specificity by removing debris from the result window. The test kit is stored in a refrigerator, but all components should sit for 30 minutes at room temperature before running the test. The result can be read 10 minutes after completing the procedure.



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Figure 4. The TnI assay is useful in helping determine if a dyspneic cat has a primary cardiac lesion or not.



“Tnl has been described as having a prognostic value, with raised plasma concentrations being associated with an increased risk of cardiovascular death, particularly in cats with HCM.”

Fanny Bernardin

non-obstructive HCM. The same study demonstrated a correlation between NT-proBNP and Tnl, as well as a correlation between NT-proBNP and various echocardiographic severity markers [12].

The Tnl assay can be considered for detection of cats with subclinical HCM provided that an assay with very high sensitivity is used (5). Affected cats have a higher serum Tnl concentration than healthy cats, and this concentration correlates with the measured left ventricular free wall thickness. Interestingly, serum Tnl concentration differs significantly between different groups (healthy cats, mild HCM, moderate HCM, severe HCM, presence or absence of arterial thrombus, decompensated vs. compensated stage, etc.)

and increases with the severity of HCM [13,14]. One study identified that a threshold Tnl value of 0.06 ng/mL could differentiate healthy cats from cats with subclinical HCM, with a sensitivity of 87.8% and a specificity of 95.4%. Sensitivity reaches 100% (with the same specificity of 95.4%) when using this threshold to differentiate healthy cats from cats with advanced subclinical HCM [15]. Note, however, that the reported sensitivity and specificity vary according to the studies, their objectives, and the threshold value used.

Biomarkers for monitoring feline cardiomyopathies

Few studies exist on the use of these two biomarkers in the follow-up of feline cardiomyopathies, and their use is described mostly as one of the steps in the diagnostic process. Tnl has been described as having a prognostic value, with increased plasma concentrations being associated with an increased risk of cardiovascular death, particularly in cats with HCM, regardless of the presence of congestive heart failure or left atrial dilatation [5,16,17]. However, regular measurements of Tnl are of only moderate value in follow-up, and provide little additional prognostic information [17].

Biomarkers in non-cardiac conditions

Because Tnl is eliminated via the kidneys, it has been shown that cats with chronic kidney disease (CKD) can have elevated Tnl values even in the

Table 1. A summary of the different uses of NT-proBNP and troponin I in the feline species.

Quantitative NT-proBNP	Qualitative NT-proBNP (rapid SNAP® test)	Troponin I
<ul style="list-style-type: none"> • Discrimination between cardiac vs. non-cardiac origin in dyspneic cats +/- pleural effusion – using plasma or pleural effusion • Discrimination between subclinical heart disease vs. healthy cat: to be considered if echocardiography not feasible. Additional examinations justified if result is abnormal. Does not exclude cardiac disease if the result is within the normal reference interval • Discrimination between occult HCM vs. healthy cat • Discrimination between obstructive vs. non obstructive HCM • Discrimination between HCM cats with CKD and hypertension vs. CKD cats without hypertension • Discrimination between cat with advanced CKD vs. early/intermediate CKD 	<ul style="list-style-type: none"> • Discrimination between cardiac vs. non-cardiac origin in dyspneic cats +/- pleural effusion – using plasma or pleural effusion, preferably diluted • Discrimination between advanced subclinical heart disease vs. healthy cat or cat with intermediate subclinical heart disease – sensitivity is better if a heart murmur is present. Additional examinations justified if result is abnormal. Does not exclude cardiac disease if the result is within the normal reference interval 	<ul style="list-style-type: none"> • Discrimination between cardiac vs. non-cardiac origin in dyspneic cats +/- pleural effusion • Prognostic value – association with risk of cardiac death • Discrimination between HCM vs. healthy cat (screening) • Aids assessment of the clinical patient – levels increase with the severity of HCM (healthy cat < cat with occult HCM < cat with advanced HCM < cat with HCM and thromboembolism). • Discrimination between compensated vs. decompensated HCM.



CONCLUSION

NT-proBNP and Tnl are an integral part of the set of complementary examinations proposed for the exploration of feline cardiac function and possible lesions. It is important not to jump to hasty conclusions when the results are obtained, but rather to consider them as pieces of a puzzle and systematically associate them as soon as possible with other additional tests, the first of which is echocardiography. Performing complementary tests, and correlating the results with the clinical findings of physical examination and the medical history, are likely to guide an informed diagnosis.

absence of a cardiomyopathy (15,18). Similarly, severe respiratory or renal impairment may result in elevated plasma NT-proBNP concentration, thereby increasing the probability of false positives (19). In cats with CKD, NT-proBNP concentrations are higher in hypertensive cats compared with healthy cats or CKD cats without an associated hypertension. Similarly, NT-proBNP concentrations are higher in cats with advanced CKD compared to other stages. It would therefore appear that NT-proBNP is a potential marker of elevated systemic blood pressure. However, in normotensive cats with mild to moderately advanced CKD, NT-proBNP concentrations were not significantly different from those of healthy cats.

Tnl has been studied in dogs for its prognostic value in critical situations requiring intensive care such as gastric torsion, systemic inflammatory response syndrome (SIRS), multi-organ failure, or piroplasmiasis (with detection of secondary myocarditis). However similar studies and data are still lacking in cats, especially for conditions such as SIRS, toxin exposure, hypoxia, anemia, and hyperthermia (4).



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SYNCOPE IN THE CAT



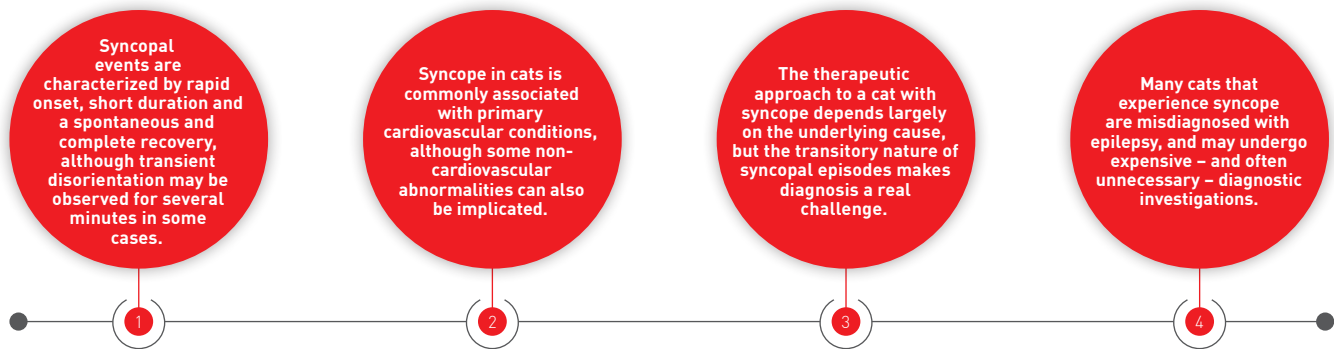
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Dr. Ferasin graduated with honors in 1992 from the University of Bologna and spent three years doing endocrinology research at the BBSRC Institute in Cambridge, gaining his PhD in 1996. After a spell as Assistant Professor at Padua University he moved to Bristol University Veterinary School as a cardiology lecturer. He was appointed Professor in Cardiology at the University of Minnesota in 2005 before returning to the UK in 2008 to work in various referral institutions. A European and RCVS Recognized Specialist in Veterinary Cardiology, his main interests include feline cardiology, exercise physiology, and the investigation and management of syncope and coughing.

How do you deal with a cat with fainting episodes? Luca Ferasin offers a step-by-step guide for the clinician.

KEY POINTS



Introduction

Syncope, or fainting, is defined as a sudden, unexpected, and unprovoked loss of consciousness followed by spontaneous recovery. Affected cats lose postural control and fall to the ground, remaining unresponsive throughout the event. However, syncope is a transient condition, usually only lasting for a few seconds, and is always followed by complete recovery. Syncopal events in people may be preceded by palpitations, dizziness, light-headedness, sweating, nausea, or even visual disturbances but, for obvious reasons, such premonitory signs cannot be communicated by pets and are therefore not reported in syncopal cats, although some pet carers will describe their cat vocalizing or “yowling” just prior to an event. A syncopal event can give the impression of sudden death, and carers who witness it are often deeply concerned, a situation comparable to the distress of parents when they see their children fainting, because they feel insecure and anxious as they are unable to help and assist their loved ones. Furthermore, cats with a history of syncope may be at increased risk of sudden death (1). Some cats may occasionally experience milder events and show signs of “pre-syncope” (or lipothymia),

characterized by falling, weakness or unsteady gait without a complete loss of consciousness. Nevertheless, the diagnostic approach and clinical management of such cases should be the same as that for investigation and treatment of complete syncopal events.

Etiology

Although several conditions can lead to syncope, this is ultimately the result of a transient global cerebral hypoperfusion. In people, irrespective of the precise underlying cause, a sudden cessation of cerebral blood flow for 6-8 seconds and/or a decrease in systolic blood pressure to 60 mmHg or less has been shown to be sufficient to cause complete loss of consciousness (2). Critical physiological values that can induce syncope in cats are not available, but it is not unrealistic to believe that they may be similar to those reported in people.

Feline syncope is often associated with primary cardiovascular conditions, although some non-cardiovascular abnormalities are also in the list of differential diagnoses. However, orthostatic,

metabolic and psychological causes of syncope, which represent common causes of fainting in people, are not typically described in veterinary medicine. Iatrogenic arterial dilation may occur after administration of drugs that induce vasodilation, such as nitroprusside, acepromazine, or amlodipine. All the abnormalities listed above can potentially induce cerebral hypoperfusion and, ultimately, loss of consciousness. A summary of potential causes of syncope is reported in **Table 1**.

In the veterinary literature, the reported cases of feline syncope have been associated with pathological variations of heart rate, such as prolonged periods of bradycardia due to sinus arrest (3) or paroxysmal atrio-ventricular (AV) block with ventricular standstill (4). Syncope in cats has also been reported with paroxysmal ventricular (VT) (5,6) or supraventricular (SVT) tachycardia (7). An episode of "tetanic seizure", possibly associated with paroxysmal atrial tachycardia, has been described in a Persian cat, although a confirmative association between syncope and tachycardia was not demonstrated in this case (8). Other syncopal reports in cats have been associated with right outflow obstruction secondary to heartworm disease (9), increases in intra-thoracic and intra-abdominal pressure with subsequent reduced venous return during defecation (situational syncope) (10), aortic dissecting aneurysm associated with systemic arterial hypertension (11), and congenital cardiac defects (12). To the best of the author's knowledge, confirmed cases of vasovagal (neurocardiogenic) syncope in cats, which is one of the most common causes of syncope in humans, have not been reported in the veterinary literature, although the author has documented a few cases during his clinical activity.

Pathophysiology

The brain needs a constant and adequate cerebral blood flow to function, and any significant reduction or interruption, even for a few seconds, can lead to syncope. Cerebral blood flow is maintained by various mechanisms affecting arterial blood pressure (BP), which is the result of cardiac output (CO) multiplied by the total peripheral resistance (TPR) (*i.e.*, $BP = CO \times TPR$). In turn, CO is determined by the volume of blood pumped by the heart (stroke volume, SV) per unit of time (heart rate, HR) (*i.e.*, $CO = SV \times HR$). Therefore, changes in either SV, HR or TPR will affect arterial blood pressure and, ultimately, cerebral perfusion.

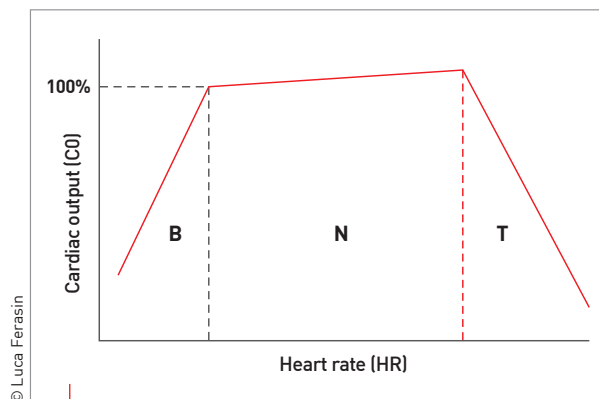
Tachycardia and bradycardia

Physiological variations in heart rate have little effect on CO. Indeed, when heart rate increases, the stroke volume decreases accordingly, since the diastolic interval is shortened, with decreased time available for ventricular filling and hence the volume of blood ejected by the heart on the following contraction. Conversely, a physiological reduction in heart rate is accompanied by a greater diastolic period and associated ventricular filling, causing increased SV. However, when changes in heart rate become pathological (*i.e.*, tachycardia and

Table 1. Potential causes of syncope in cats.

Cardiovascular
<ul style="list-style-type: none"> Anatomical outflow obstruction (severe aortic or pulmonic stenosis; heart base or intracardiac tumors) Myocardial disease (hypertrophic cardiomyopathy (HCM), ischemia, myocarditis) Bradycardia (<i>e.g.</i>, atrio-ventricular (AV) block, atrial standstill, asystole) Tachycardia, supraventricular (SVT) or ventricular (VT)
Vascular
<ul style="list-style-type: none"> Orthostatic hypotension (venous pooling) * Neurocardiogenic (vasovagal) Hypovolemia/dehydration Situational (straining during coughing, defecation, micturition, swallowing, vomiting)
Non-cardiovascular
<ul style="list-style-type: none"> Neurological (<i>e.g.</i>, seizure disorder, head trauma, brain lesion) Metabolic (severe hypoglycemia) * Psychological (anxiety, panic) * Iatrogenic (<i>e.g.</i>, acepromazine, hydralazine, amlodipine, nitrates) Miscellaneous (<i>e.g.</i>, pacemaker failure)

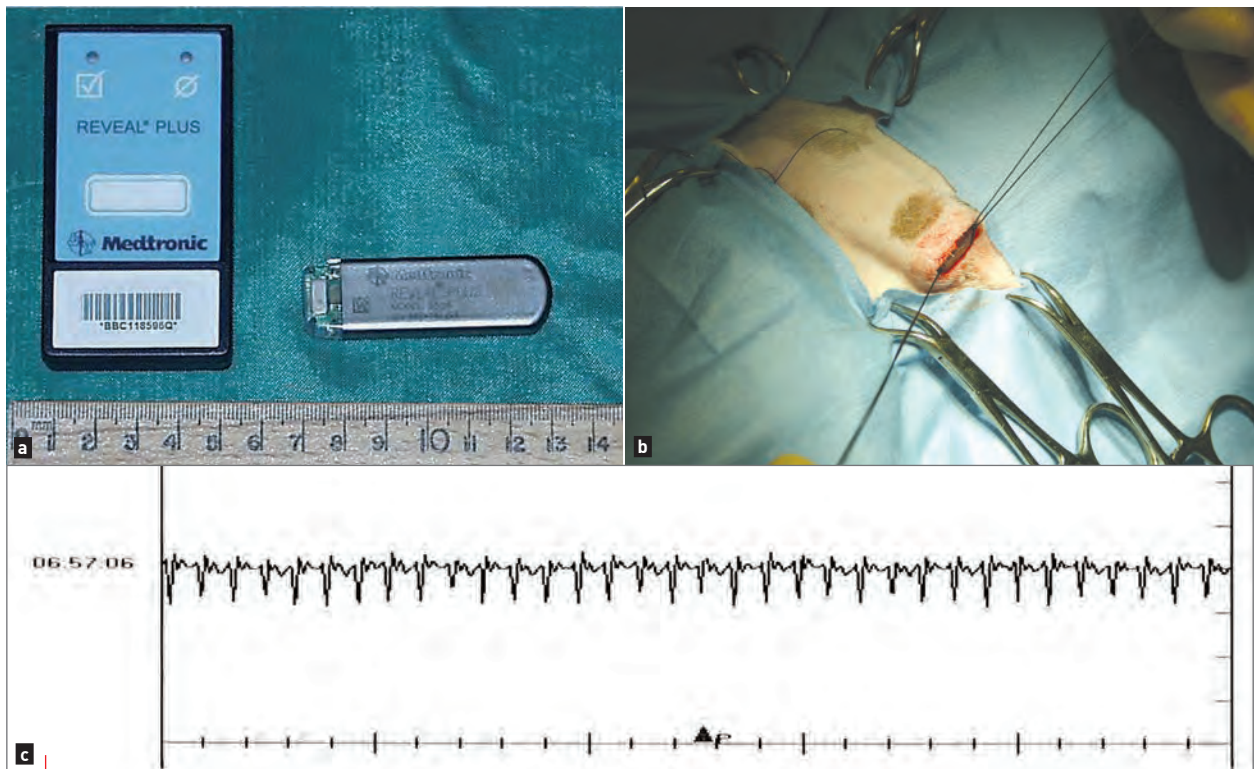
* - uncertain if this occurs in cats



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Figure 1. The relationship between cardiac output (CO) and heart rate (HR) (26). The interval "N" represents physiological variations of heart rate (*e.g.*, during exercise) where the cardiac output remains almost unchanged, as increased HR reduces the stroke volume (SV) in a harmonized manner ($CO = SV \times HR$). However, when HR increases above the physiological range (interval "T" = tachycardia) the diastolic time decreases significantly and becomes insufficient to provide adequate ventricular filling and SV, consequently compromising the CO. Vice versa, when HR drops excessively (interval "B" = bradycardia), the ventricular filling, despite a prolonged diastolic time, does not increase proportionally due to the limited ventricular compliance, which compromises the SV and, eventually, CO.

bradycardia), CO drops significantly with both conditions. Indeed, rapid and sustained tachycardia can critically reduce diastolic time to the point that stroke volume becomes severely affected. Conversely, a profound bradycardia, despite the increased ventricular filling, can lead to a reduced CO (**Figure 1**). Examples of syncopal events induced by rapid tachycardia and profound bradycardia are reported in **Figures 2 and 3** respectively.



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Figure 2. Nine-year-old male neutered Devon Rex cat referred with a long history of syncopal episodes, occurring approximately every 3-4 months. Resting and 24-hour Holter ECG recordings, thoracic radiographs and echocardiograms were inconclusive. An implantable loop recorder **(a)** was therefore surgically inserted subcutaneously on the left side of the chest to allow continuous ECG monitoring **(b)**. A few weeks later the cat experienced another syncopal episode and the carer managed to trigger the patient activator device. The ECG trace during the syncopal event showed rapid supraventricular tachycardia (SVT) at a rate of 430 bpm (black arrowhead) **(c)**. The cat was treated with sotalolol (10 mg PO BID) and did not experience any further fainting episodes.

Outflow obstruction

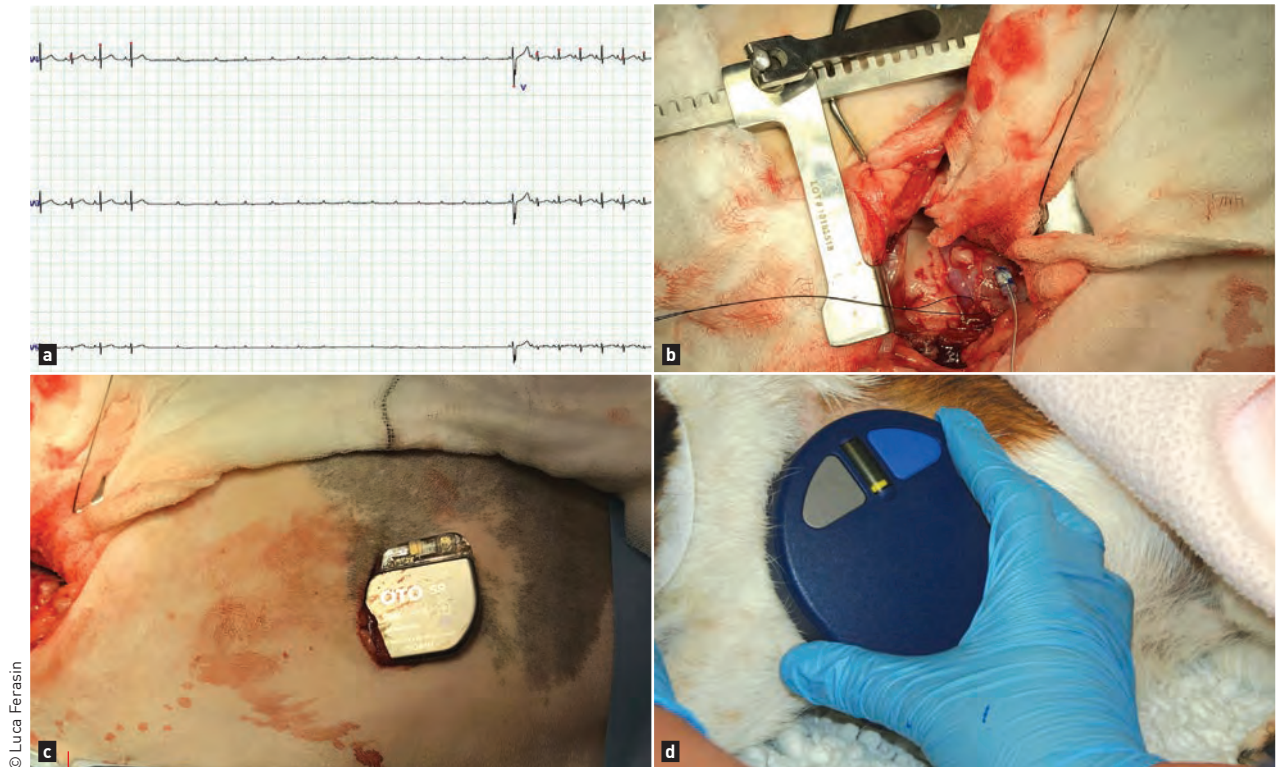
The pathophysiological mechanism of syncope secondary to outflow obstruction is rather intuitive, since any clinical condition that significantly reduces SV will cause a drop in CO. Congenital abnormalities, such as aortic and pulmonic stenosis, can potentially cause severe left and right outflow obstruction respectively, often accompanied by exercise intolerance and syncopal events. However, the most common form of outflow obstructions in cats is represented by dynamic left ventricular outflow tract obstruction secondary to systolic anterior motion (SAM) of the mitral valve, which is frequently observed with hypertrophic cardiomyopathy (HCM) [13], although this abnormality can also be observed in the absence of left ventricular hypertrophy (LVH) [14]. However, syncope secondary to SAM is seldom observed in cats, unlike in humans where fainting episodes are commonly observed in severe SAM, with or without concomitant LVH [15,16]. Dynamic right ventricular outflow tract obstruction (DRVOTO) is another common finding in feline patients, although this condition appears to be completely benign in this species [17,18] and not associated with fainting. Syncope secondary to outflow obstruction in cats has also been observed in cases of heartworm disease [9] and severe aortic stenosis (**Figure 4**).

Myocardial disease

Myocardial disease, such as HCM and arrhythmogenic right ventricular cardiomyopathy (ARVC), can cause cardiac syncope both in people and cats [1,13,19]. Although cardiac arrhythmias may play a pivotal role in the onset of syncope in myocardial disease, myocardial failure should also be taken into consideration. In HCM for example, the diminished left ventricular filling volume and impaired contractility secondary to myocardial hypertrophy, disorganization of the myocyte fibers, myocardial scarring, and fibrosis can severely affect CO, resulting in diminished blood flow to intramural coronary vessels (and the rest of the body), causing intramural myocardial infarctions. In ARVC, the presence of fibro-fatty replacement of the right ventricle can cause right ventricular dilation and ventricular aneurysm, with significant systolic dysfunction and consequent drop in CO. Similarly, all end-stage forms of cardiac disease will eventually be accompanied by myocardial dysfunction, reduced cardiac contractility and ultimately a decline in CO.

Neurally mediated syncope

This is the most common type of syncope in people, comprising approximately 45% of cases [20], but it is relatively uncommon in cats. It can be vasovagal, situational, or secondary to carotid sinus



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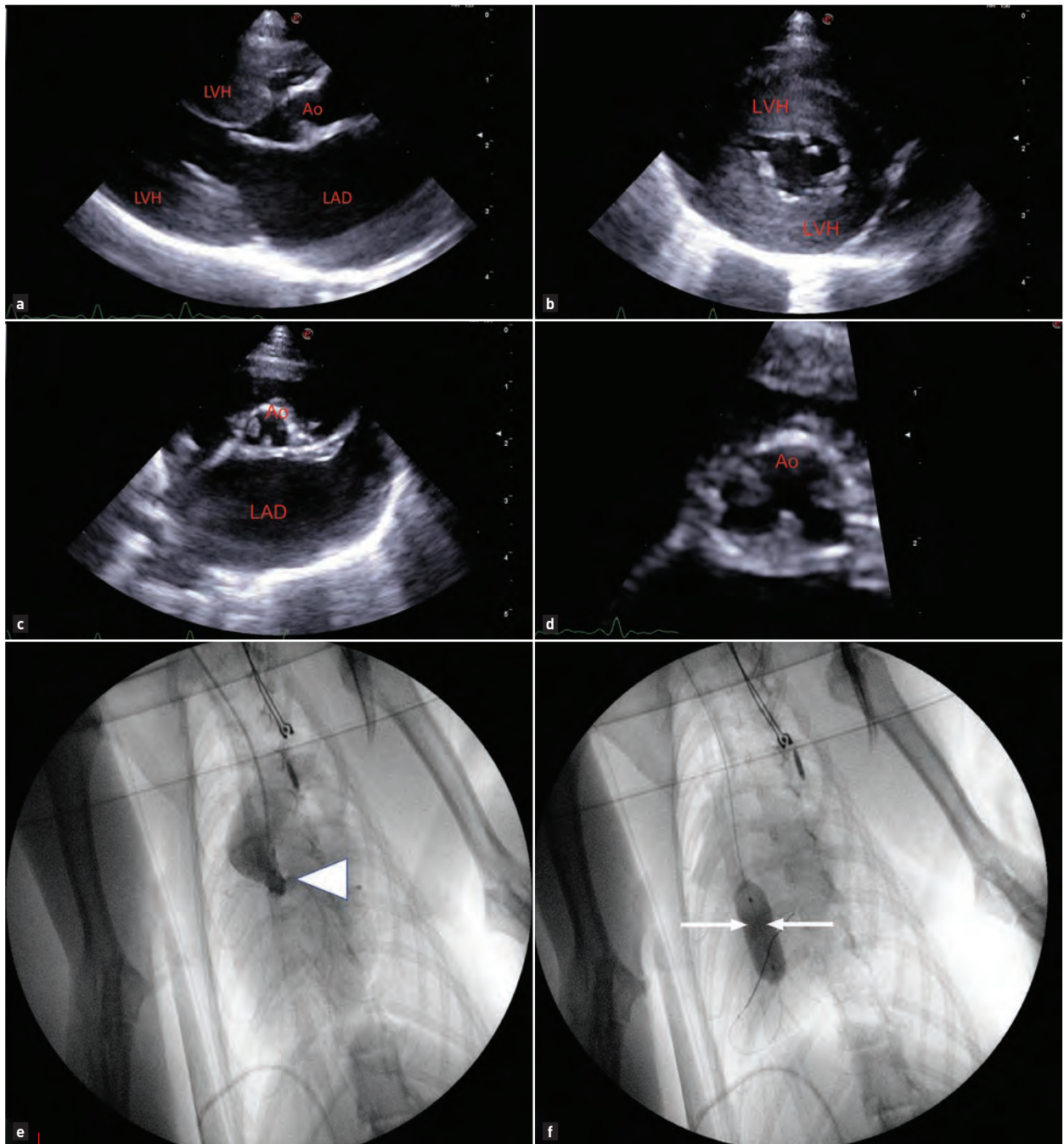
Figure 3. Eleven-year-old female neutered Domestic Shorthair cat, initially referred for neurological work-up following onset of daily episodes of tremors, facial twitching and fainting. Prolonged cardiac pauses were detected during clinical examination, which prompted an immediate cardiac workup; echocardiography, thoracic radiography and resting ECG were unremarkable, but 24-hour Holter monitoring showed predominant sinus rhythm alternating with periods of atrio-ventricular (AV) dissociation, with an average daily rate of 93 bpm. The falling and twitching episodes coincided with periods of complete AV block with ventricular standstill, the longest period lasting approximately 8 seconds (a). A permanent pacemaker was surgically implanted, with a lead sutured to the left ventricular epicardium (b). The epicardial lead was tunneled under the lateral thoracic wall muscles and the pulse generator was inserted in a subcutaneous pocket created over the left cranioventral abdominal wall (c). Syncopal episodes did not represent following the procedure and device interrogation (d), performed six months later, revealed that the pacemaker was intervening 24% of the time to avoid cardiac pauses and associated fainting episodes.

hypersensitivity. The pathophysiology of neurally mediated syncope is rather complex, and originates from an increased sympathetic tone, which can sensitize and facilitate the activation of cardiac mechanoreceptors that occurs with very vigorous ventricular contraction or by C-fibers activation secondary to myocardial ischemia and reperfusion. The activation of these receptors triggers an abrupt centrally mediated reduction in sympathetic activity, with concomitant parasympathetic activation, resulting in vasodilation and bradycardia and, ultimately, a rapid and profound hypotension [21]. An example of vasovagal syncope in a cat is shown in **Figure 5**.

Situational syncope has been reported in a cat following defecation [10]. The mechanism is likely associated with the increased intrathoracic and intrabdominal pressure during defecation, which tends to reduce venous return and subsequently SV and CO. This cat had a history of straining prior to fainting, which may have activated tension receptors in the intestinal wall, resulting in sudden hypotension and bradycardia. In people, situational syncope is also observed during or immediately after urination, defecation, coughing or swallowing, with a mechanism similar to the one explained above.

●●● Diagnosis

The transitory nature of episodes and spontaneous resolution of clinical signs represent a real diagnostic challenge. In humans with no abnormalities reported on the clinical history or physical examination, diagnosis may not be achieved in around 50% of cases [22], and similar figures are reported in small animal practice. An excellent understanding of the efficacy and utility of the investigational tools for syncope is therefore required in order to institute appropriate management promptly and efficiently. In fact, a wrong choice of sequential tests may result in poor diagnostic yield and unnecessary costs. Furthermore, a delayed diagnosis may result in sudden death [23]. Collecting the patient's history in a thorough and consistent manner is fundamental, and appropriate questions should be formulated to understand whether or not the patient is experiencing syncopal events. Indeed, cat carers will often only report a vague description of "collapsing" events, so the clinician should determine if the reported episodes are accompanied by transient loss of consciousness. Syncopal events should also be characterized by rapid onset, short duration (typically no longer

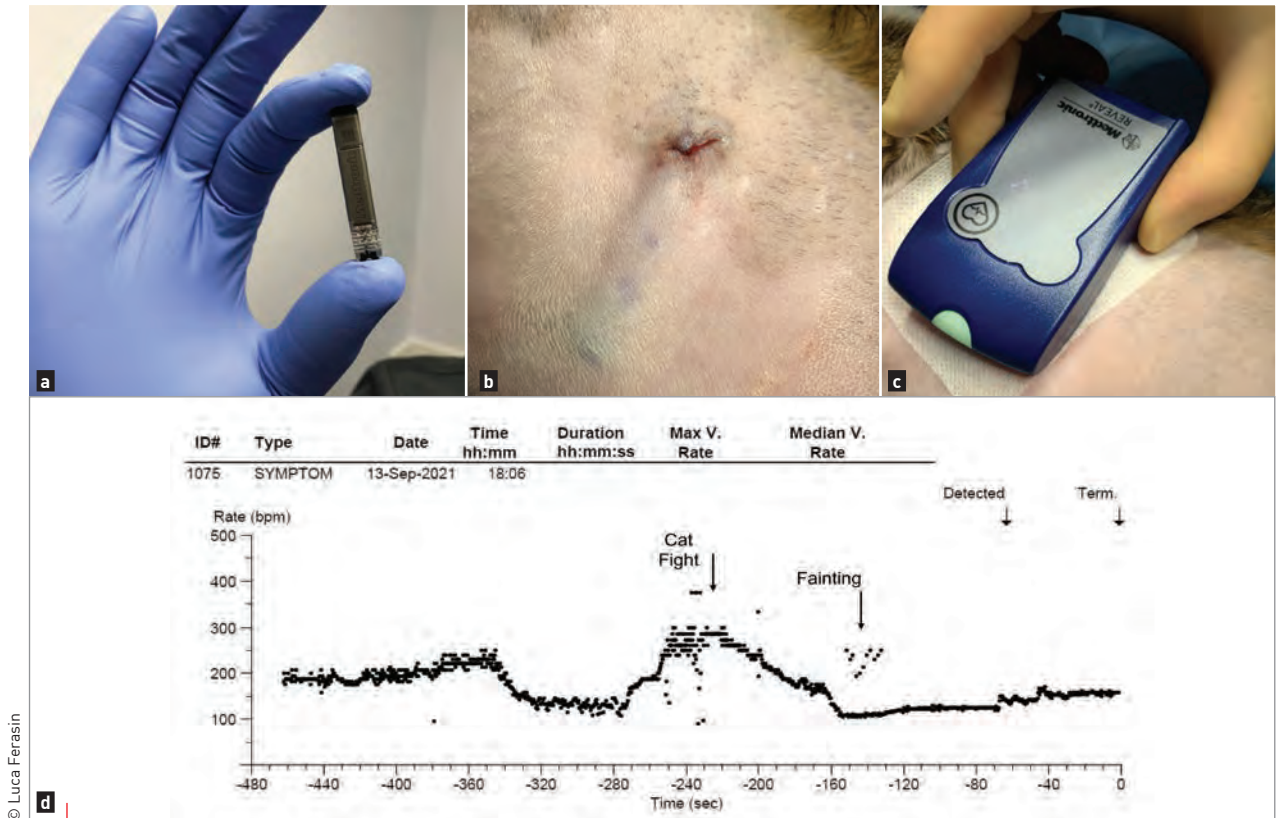


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Figure 4. Three-year-old female Bengal cat with a history of syncopal episodes following excitement during playing. The cat was diagnosed with a severe form of valvular aortic stenosis (pressure gradient 118 mmHg) causing left ventricular concentric hypertrophy and left-sided congestive heart failure. Echocardiographic images were obtained from right parasternal views in long axis view 5-chamber (**a**), short axis at the level of the papillary muscles (**b**), and short axis at the level of the heart base (**c and d**). This showed significant left ventricular concentric hypertrophy (LVH), left atrial dilation (LAD) and thickened and partially fused aortic valve cusps (Ao), which are responsible for the stenotic lesion. Images (**e**) and (**f**) were obtained on fluoroscopic guidance during balloon valvuloplasty to palliate the magnitude of the aortic stenosis. The stenosis is highlighted during selective angiography (**e**, white arrowhead), while the inflated balloon (**f**, white arrows) indicates the successful dilation of the stenotic valve.

than 20 seconds) and followed by a spontaneous and complete recovery, although transient disorientation may be observed for several minutes in some cases. Information obtained from carers should include any history of cardiac disease or medications that may induce arrhythmias or hypotension, the number and frequency of the episodes (in full detail), identification of

precipitating or trigger factors, including a detailed description of physical activity, time of the day, environmental conditions, degree of excitement, etc., prior to or at the time of the episode. It is important to accurately quantify the type and duration of the event and obtain information (when available) about the color of mucous membranes and heartbeat during the episodes. Lethargy,



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Figure 5. Five-year-old male neutered Domestic Shorthair cat with syncopal episodes observed following periods of stress or excitement, such as fighting with other cats in the garden. The cat was experiencing episodes approximately every 3-4 weeks and was initially referred for a neurological assessment, which was unremarkable. A cardiology workup was therefore requested. Echocardiography was unremarkable, with the exception of a significant dynamic left ventricular outflow obstruction (LVOTO) caused by systolic anterior motion (SAM) of the mitral valve. Standard ECG recording showed normal sinus rhythm with a heart rate of 180 bpm, and 24-hour Holter recording failed to identify any abnormalities, revealing only normal sinus rhythm with an average daily rate of 166 bpm (range 88-244 bpm). However, no syncopal events occurred during the recording period. Empiric treatment with atenolol (6.25 mg PO SID) showed no significant response, so the dose was increased to 6.25 mg PO BID, which resulted in an even more frequent occurrence of fainting episodes. An implantable loop recorder (ILR) (a) was then surgically inserted subcutaneously on the left side of the chest to allow continuous ECG monitoring (b). The device functionality was tested during the procedure using a pacemaker programmer and dedicated patient activator device (c). ILR interrogation following another fainting episode showed a period of tachycardia during a cat fight, followed by a sudden drop-in heart rate, from approximately 300 bpm (“Cat Fight”) to 100 bpm (“Fainting”). The carers heard the fight and, finding their cat unconscious on the ground, immediately activated the patient activator device (“Detected”), which saved the ECG recording throughout the event (d). The tachogram (RR interval time series) from the ECG is compatible with a vasovagal (neurocardiogenic) syncope. The carer was advised to discontinue atenolol and to avoid stressful events, such as interaction with other cats, which resulted in complete disappearance of the syncopal episodes.

disorientation or behavioral changes following a collapse, frothing at the mouth, unconsciousness lasting for more than a few minutes, or an absence of pale or cyanotic mucosa would suggest seizures or a neurological etiology rather than syncope. Nevertheless, patients experiencing prolonged syncopal events may also lose sphincter control, with subsequent involuntary defecation and/or urination, and can also display tonic-clonic activity and opisthotonos, mimicking seizures (24). For this reason, many cats experiencing syncope are misdiagnosed with epilepsy and undergo expensive and often unnecessary diagnostic investigations, sometimes involving general anesthesia. Therefore, it is important to understand what happens before, during and after a falling event in order to distinguish, as much as possible, between these two similar presentations. In such cases an owner’s

detailed diary of events and video recording of falling episodes, even using a mobile phone camera, can be extremely helpful.

A full physical examination, with a particular emphasis on the assessment of the neurological and cardiovascular systems, is probably the most important component of the evaluation of a patient with suspected syncope (25). Physical examination should be conducted in a thorough and consistent manner, paying particular attention to assessment of the cardiovascular system (including blood pressure measurement), level of hydration, and presence of concomitant neurological or musculoskeletal abnormalities. Any cardiac arrhythmia, murmur, or gallop sounds would be highly suggestive of an underlying heart abnormality, and should justify a complete cardiac evaluation.

Laboratory tests (basic hematology and serum biochemistry) have a low diagnostic yield, although they are important to rule out severe anemia, dehydration, electrolyte imbalances and musculoskeletal lesions. Measurement of cardiac troponin I may reveal elevations consistent with an underlying myocardial insult, including ischemia and myocarditis. Elevated thyroxine (T4) would suggest hyperthyroidism, which can potentially cause cardiotoxicity.

Echocardiography should be considered if there are abnormal cardiac findings during the physical examination, or where there is a familial history/predisposition of cardiac disease. However, the majority of fainting cats have unremarkable echocardiographic findings. Resting electrocardiography (ECG) identifies the reason for fainting in only in a small percentage of patients. Indeed, sporadic syncope may reflect the episodic nature of an underlying ECG abnormality, which is often missed even on a five-minute continuous recording, therefore prolonged ECG monitoring can represent a more successful diagnostic tool. Nevertheless, even 24/48-hour Holter recording has a relatively low diagnostic value, especially when the falling episodes occur occasionally and can be missed during the recording. The only exception for justifying Holter monitoring is for fainting episodes occurring several times a week (19). Alternatively, 7/14 day monitoring, which is available only with a limited number of recorders, has a higher chance of achieving a conclusive diagnosis (25), but diagnostic yield increases dramatically if an implantable loop recorder (ILR) is used. Reliability and accuracy of ILRs has been reported in the veterinary literature with excellent results (7,23); for cats with unexplained syncopal episodes, the manually activated ILR can provide invaluable diagnostic and prognostic information by either confirming or disproving the association between syncope and arrhythmias or conduction abnormalities. If a syncopal event is observed and the tests listed above (including ILR) are inconclusive or not suggestive of a cardiac etiology, then other investigations should be considered, including abdominal ultrasound (to rule out internal bleeding), advanced imaging (MRI, CT), electromyography (EM), electroencephalography (EEG), and cerebrospinal fluid (CSF) collection.

Management

Treatment of a cat with syncope has three main goals: avoiding sudden death and prolonging survival, avoiding traumatic injuries sustained during a falling event, and preventing further syncopal events. The therapeutic approach depends largely on the cause and mechanism of the syncope. If a definitive diagnosis has not yet been achieved, carers should be instructed to keep their cat indoors to avoid potential trauma that may occur if the pet is left unsupervised. However, if a diagnosis has been obtained, therapy should be aimed at controlling the underlying primary

condition responsible for the transient loss of consciousness. For example, treatment of sustained or paroxysmal rapid ventricular and supraventricular tachycardia can be attempted with anti-arrhythmic medications such as oral atenolol and sotalol. Diltiazem has no effect on ventricular arrhythmias but can be considered for supraventricular arrhythmias. However, all these drugs can also significantly decrease resting heart rate and affect stroke volume and cardiac output, potentially precipitating congestive heart failure in patients with underlying myocardial disorders. Therefore, it is important to consider 24-hour Holter recording a few days after starting anti-arrhythmic therapy in order to monitor the appropriate response to treatment and possible residual presence of paroxysmal tachycardias.

The appropriate treatment for most cats with syncope associated with bradycardia would be a permanent pacemaker implant. Although transvenous pacing lead placement into the right ventricular apex is the most common method of pacemaker implantation in dogs, cats appear predisposed to complications, such as cranial vena cava syndrome with chylothorax, right ventricular outflow tract obstruction, and intracardiac thrombosis (4,26). Therefore, surgical epicardial lead placement via thoracotomy is currently the most commonly adopted technique for pacemaker implantation in cats, and is generally successful with few minor complications.

Fixed outflow obstructions, such as aortic and pulmonic stenosis, can be palliated with balloon valvuloplasty, a minimally invasive intervention using a catheter with a balloon on its tip that can be inflated at the level of the stenotic valve to stretch and open the partially fused cusps. Dynamic outflow obstructions are very rarely associated with syncope in cats, but if a cause-effect relationship can be documented, therapy with beta blockers (e.g., atenolol) can be attempted to reduce the magnitude of the obstruction.

Therapy for neurally mediated syncope is seldom necessary. A careful history collection with attention focused on identifying precipitating factors should reveal the triggering events (e.g., stress, excitement), and avoidance of these circumstances is usually sufficient to drastically reduce the frequency and severity of fainting episodes. Situational syncope can be successfully controlled by addressing and eliminating, when possible, the underlying condition (e.g., coughing or straining during micturition and defecation). Pacemaker implant represents a controversial solution for neurally mediated syncope, but may be considered if the fainting event is caused by very long cardiac pauses. The major limitation here is that the pacemaker cannot control the systemic hypotension associated with the sudden vagally induced vasodilation, so it should be programmed with specialized pacing algorithms such as heart rate hysteresis; this allows the pacemaker to start ventricular pacing only if the



CONCLUSION

A cat which presents with episodes of falling/fainting can be a diagnostic challenge, and a logical approach to history-taking, examination and diagnostic testing is essential. The majority of cats with syncope will have a primary cardiac etiology, although other causes can and do exist. Ultimately therapy should be aimed at prolonging survival (and hence averting sudden death), avoiding injuries from falling, and preventing further syncopal events, but the therapeutic approach depends largely on the cause and mechanism of the syncope. It is, however, vital not to misdiagnose syncope for seizures, which requires a completely different approach and may carry a different prognosis.

spontaneous heart rate falls below a critical level, whereby pacing continues at a selected higher rate unless intrinsic ventricular activity is sensed. The intention is that when an event occurs, the higher rate of artificial pacing may compensate for the hypotension caused by the sudden reduction in total peripheral resistance.

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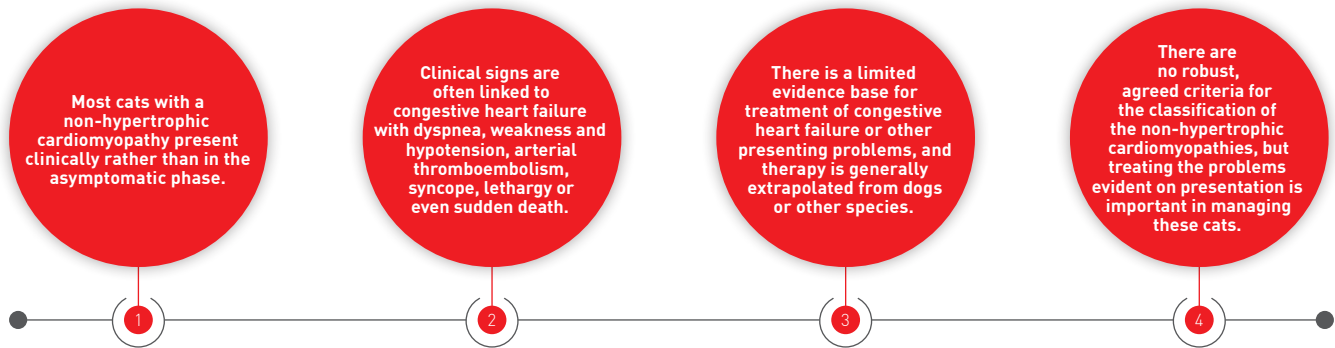
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MANAGEMENT OF THE CAT WITH HEART FAILURE

Cats with cardiomyopathies other than hypertrophic cardiomyopathy often first present with severe or even life-threatening clinical signs; this article focuses on the diagnosis of the underlying cardiac condition and the options for treatment.

KEY POINTS



Introduction

Feline patients with cardiomyopathies other than hypertrophic cardiomyopathy (HCM), often referred to as non-hypertrophic cardiomyopathies (nhCM), rarely present to the veterinarian with preclinical disease. This is because examination during the preclinical phase is usually unremarkable, in contrast to the frequency of heart murmur detection in the cats with preclinical HCM. Cats with nhCM or end-stage HCM may present in different ways and with a variety of signs, but because they are sedentary and excellent at hiding subtle illness from their owners, the clinical onset in an affected cat may be acute. Signs can be linked to congestive heart failure (mainly severe dyspnea), cardiogenic shock (with weakness and hypotension), aortic thromboembolism (with severe pain and loss of use of one or more limbs), or arrhythmias (which may result in weakness, syncope or sudden death).

Management of the patient is directed towards the presenting problem(s), and this article will mainly address these strategies. Once the patient is stable, further investigations, especially echocardiography, should give the diagnosis of the primary cardiomyopathy, but this may not significantly affect the palliative management in most cases. Investigations should actively exclude other systemic conditions which may result in a

cardiomyopathy phenotype and clinical presentation, such as hyperthyroidism, systemic hypertension, acromegaly, transient myocardial thickening, myocardial infiltration (e.g., lymphoma), myocardial infarction, tachycardia induced cardiomyopathy etc. It is beyond the scope of this article to discuss these further, but these conditions must be actively excluded. The article will then briefly review current guidance on the diagnosis of the primary cardiomyopathies other than HCM in cats (1,2) and how they are identified echocardiographically.

Congestive heart failure (CHF)

Cats with CHF typically present with severe dyspnea, usually because of fulminant pulmonary edema and/or pleural effusion. Pleural effusion in cats can be due to left-sided, right-sided or biventricular CHF, and is important to recognize (e.g., via thoracic point of care ultrasound (T-POCUS) during triage on presentation) as thoracocentesis is both lifesaving and of diagnostic purpose. The pleural effusion associated with CHF is usually a modified transudate, but it may be chylous. During T-POCUS, left atrial (LA) size should be subjectively determined; if it appears normal, it is highly unlikely that the dyspnea is associated with CHF. The presence of B-lines [hyperechoic radial lines within the lung-field, indicating a mix of fluid- and



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Catheryn Partington

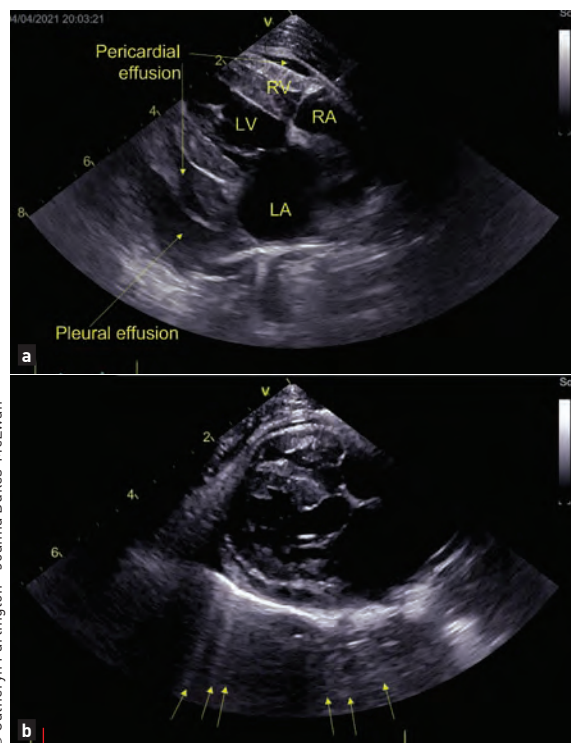
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Dr. Partington graduated from the University of Liverpool in 2014, having also attained a Masters in Veterinary Science, and returned to the University for both her rotating internship and cardiology residency, completing the latter in 2021. She has also worked in first opinion and emergency practice and is now studying towards ECVIM-CA cardiology Diplomate status. She has a passion for feline cardiomyopathies and was recently appointed clinical cardiologist at the University of Cambridge, where she also finds time for clinical research and teaching.

air-filled alveoli) in association with LA enlargement is most likely to reflect cardiogenic pulmonary edema (**Figure 1**). Decompensation into fulminant pulmonary edema may be precipitated by a stressful event, anesthesia, intravenous fluid administration or steroid administration. Decompensation of an existing cardiomyopathy may also be associated with concurrent illness, especially if this results in volume overload or high output states (e.g., anemia, hyperthyroidism). Cats with predominantly right-sided CHF (R-CHF) (ascites, pleural effusion and (very rarely) subcutaneous edema) are more likely to have arrhythmogenic right ventricular cardiomyopathy, but it is possible in other cardiomyopathies with myocardial failure. Examination of the jugular veins is informative; distension and the hepatojugular reflux is consistent with R-CHF, but a large volume of pleural effusion (even non-cardiogenic) can also result in jugular distension in this species.

Emergency treatment of pleural effusion

When there is dyspnea due to significant pleural effusion, this must be drained. Sedation may not be required, but if the cat is very anxious or stressed, butorphanol (**Table 1**) can be beneficial. Supplemental oxygen should be provided. Ideally, the assessment and procedure should be carried out with the cat sitting in sternal recumbency. Clip and aseptically prepare one side of the chest at the costochondral junction, around the 7th-8th intercostal space; the site can be ultrasound guided. Using a 21G butterfly catheter attached to a three-way tap or one-way centesis valve and a 10 mL syringe, perform thoracocentesis. Local anesthetic can be used but generally causes more discomfort than directly inserting the butterfly needle into the chest.



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Figure 1. T-POCUS evidence for CHF in the cat. **(a)** is a right parasternal (RPS) long axis 4 chamber view showing a pleural and a small pericardial effusion. The left atrium is subjectively dilated. **(b)** is a RPS long axis 4 chamber view showing B-lines beyond the pericardium-lung interface (arrows). These are hyperechoic radial lines extending through the lung tissue, showing a mixture of air and fluid in the pulmonary parenchyma. They can also be appreciated on lung ultrasound away from the heart. The left atrium is subjectively dilated in this image.

At least 300 mLs of effusion can usually be removed, and one-sided thoracocentesis will normally drain the pleural effusion adequately, but if needed, the opposite side can also be drained.

Retain some fluid for total protein, nucleated cell count and cytological and other evaluation, especially at initial presentation. Cats are likely to have concurrent pulmonary edema, so treatment with diuretics is essential.

Emergency treatment of pulmonary edema

Not all cats with pulmonary edema will have pulmonary auscultation abnormalities such as crackles, but if auscultation identifies a murmur, diastolic gallops or an arrhythmia, this is suggestive of CHF. T-POCUS identifies LA enlargement and B-lines. The dyspneic cat is very fragile, and gentle, stress-free handling is required to assist stabilization prior to investigations; butorphanol may be given for anxiolytic benefit. Provide the cat with flow-by oxygen or place in an oxygen cage as soon as initial triage and treatment have been completed. If cardiogenic pulmonary edema is strongly suspected, give furosemide (which administered intravenously has an initial venodilator effect, reducing preload) and repeat as required while monitoring respiratory rate and effort.

Addition of nitroglycerine (glyceryl trinitrate; GTN) may be considered. It is a venodilator, so preload reduction and decreasing left atrial pressure may help alleviate pulmonary edema. If there are signs of myocardial failure or cardiogenic shock, pimobendan IV or dobutamine as a constant rate infusion can be considered (see cardiogenic shock section). **Table 1** summarizes all drugs and doses.

Chronic management of feline CHF

There is very little evidence for treating cats with CHF, so knowledge is typically extrapolated from what we know in other species [3]. Other than furosemide, most drugs used to manage feline cardiomyopathies are not licensed in the species or for the treatment of CHF (**Table 1**). However, there is anecdotal evidence and expert opinion supporting use of some of these drugs. Using the ABCD classification, cats with CHF are Stage C. Stage D is refractory CHF [1].

Compliance (feline or owner) is frequently an issue when medicating cats. It is therefore important that the priority of each drug is clear to the client – e.g., diuretics are essential, other drugs may not be. The more drugs prescribed, the less compliance is likely to be, and the clinician needs to consider this, especially when there is limited evidence supporting many of the drugs used.

Diuretics

Diuretics are essential in the management of CHF, and will be required long term for most stable cats once acute decompensation has been treated, with

furosemide being most commonly prescribed. During chronic therapy, the furosemide dose should be slowly down-titrated, with home-monitoring of sleeping respiratory rate (SRR), to aim for the minimum effective daily dose which controls clinical signs. The dose should be up-titrated if the owner notes a persistent increase in SRR. Cats with severe CHF may require high doses of furosemide, so the dose range is considerable. As a ceiling-loop diuretic, it results in loss of chloride, sodium and potassium (with water) in the renal tubules, so pre-renal azotemia and hypokalemia may subsequently develop. In cats with pre-existing chronic kidney disease (CKD), the addition of pre-renal with renal azotemia is problematic. As a minimum monitoring check, serum urea, creatinine and electrolytes should be evaluated one week post-furosemide dose increase. Hypokalemia may result in weakness or worsen the risk of arrhythmias. Hypochloremia is an expected side effect of furosemide. Hyponatremia does not usually occur, unless there is intense neuroendocrine activation associated with severe CHF or as a consequence of furosemide administration. Hyponatremia is dilutional, as a consequence of high vasopressin resulting in free water retention.

Drugs to counteract neuro-endocrine activation

Although much less studied than in other species, reduced cardiac output will result in neuro-endocrine activation, which results in progression of CHF. Initially, reduced blood pressure results in sympathetic stimulation, with beta-receptor stimulus resulting in tachycardia, increased myocardial contraction and increased risk for arrhythmias. Alpha-receptor stimulation will result in vasoconstriction, increasing pre- and after-load. Renin release and activation of the renin-angiotensin-aldosterone system (RAAS) ultimately results in angiotensin II and aldosterone release. Both angiotensin II and aldosterone result in myocardial remodeling and fibrosis. Angiotensin II is a potent vasoconstrictor and triggers increased vasopressin and endothelin release. Aldosterone causes increased sodium and water retention and the CHF syndrome. There is evidence for RAAS activation in cats with HCM or after therapy with some drugs, including furosemide [4]. Therefore, in cats with CHF requiring furosemide, it is logical to also start treatment to counteract the RAAS system, such as an angiotensin-converting enzyme (ACE) inhibitor (e.g., benazepril) or an angiotensin II receptor (AT1) blocker (e.g., telmisartan) and/or an aldosterone antagonist (spironolactone). However, evidence is currently lacking that ACE-inhibitors influence progression of feline cardiomyopathies or survival time [5]. One study suggested a possible benefit in cats with CHF receiving enalapril, but this was not statistically significant [6]. Most of the feline cardiomyopathies result in diastolic heart failure, which in human medicine also lacks strong evidence about efficacy of treatments other than diuretics.



“Compliance (feline or owner) is frequently an issue when medicating cats. It is therefore important that the priority of each drug is clear to the client – e.g., diuretics are essential, other drugs may not be.”

Joanna Dukes-McEwan

Telmisartan (AT1 blocker) is licensed in some countries for feline renal disease, but so far no studies have reported its use for CHF, although evidence in cats suggest a favorable effect on RAAS (7). A palatable liquid formulation facilitates medicating cats if counteraction of RAAS is indicated.

The aldosterone antagonist spironolactone is a mild diuretic, counteracting sodium and water retention. Spironolactone made no difference to diastolic function or ventricular mass in Maine Coons with preclinical HCM (8) but in contrast, one small study in cats with cardiomyopathy and CHF, all receiving furosemide and benazepril, suggested that the addition of spironolactone reduced morbidity and mortality (9).

Inotropic support and balanced vasodilation

Pimobendan (**Table 1**) is an inodilator drug, which improves pump function by calcium sensitization and phosphodiesterase III inhibition. It is also a balanced vasodilator, reducing afterload and preload, and improves myocardial function without increasing myocardial oxygen consumption. It is indicated in cardiomyopathies associated with impaired systolic function, especially dilated cardiomyopathy (10,11). Positive inotropes and arteriodilator drugs are theoretically contraindicated in HCM with left ventricular outflow tract obstruction (LVOTO), since the combination of increased contraction and arteriodilatation may increase the severity of LVOTO. However, a retrospective case-control study of cats treated with CHF associated with HCM including some with LVOTO showed an increased survival time in cats receiving pimobendan (12). LVOTO did not result in increased adverse events in another study (13); in contrast, a prospective study failed to show any survival benefit for cats with CHF receiving pimobendan (14).

Pimobendan may improve LA function, which may in turn reduce the risk for thromboembolic complications (15), and it has been reported to

inhibit platelet aggregation, although this may only be at doses much higher than the clinical recommendation (16).

Diltiazem is licensed in some countries to treat feline HCM and has been advocated as a treatment to improve diastolic function, but interim analysis of one study showed no additional benefit of diltiazem compared with furosemide alone (6,17). Its major indication is an antiarrhythmic drug (**Table 1**).

Beta blockers

If a cat is receiving beta-blockers (e.g., for previously diagnosed HCM with LVOTO), the dose should be carefully down-titrated or even stopped after a few weeks. This is because the intense neuroendocrine activation of CHF includes increased sympathetic drive to maintain cardiac output; beta-blockade may prevent some of this compensatory effort. However, the decision about discontinuing beta-blockers depends on each individual case (e.g., if there is significant LVOTO). Beta-blockers should never be started in a cat presenting with uncontrolled CHF; an interim analysis of heart failure treatments indicated significantly reduced survival in cats receiving this class of drug (6).

What about refractory CHF?

In a cat with poorly controlled or recurrent CHF signs that is already receiving a high dose of furosemide, an underlying end-stage cardiomyopathy is likely. If the cat is in R-CHF, bowel edema may lead to impaired absorption of oral medications, as well as development of cardiac cachexia. Briefly, some options for refractory CHF (**Table 1**) include:

- Swap furosemide for torasemide, a much more potent ceiling loop diuretic with higher bioavailability; it may only need to be given once a day and is well tolerated (18). The total daily dose of furosemide can be divided by 10 (or 20) for a starting dose of torasemide, but renal function and electrolytes must be monitored since the risk of causing acute kidney injury is high.
- Consider sequential nephron blockade with the addition of hydrochlorothiazide (often combined with amiloride). This can be especially useful in refractory R-CHF.
- Optimize all CHF medication, including addition of pimobendan, ACE-inhibitors, and spironolactone.

What about cats with CKD and CHF?

A cat with concomitant CKD may become more azotemic if relatively high doses of furosemide are required to manage its CHF. This is a grave prognostic indicator, as the cat tends to see-saw between uncontrolled CHF and worsening azotemia, depending on the dose of furosemide. It often prompts euthanasia if a balance cannot be achieved.

It is not uncommon in the cat with severe CHF requiring high initial cumulative furosemide doses to control the CHF to cause an acute kidney injury.

Table 1. Suggested drugs and doses for treatment of feline cardiomyopathy manifestations.

Severe left sided congestive heart failure (Stage C)	
Furosemide	<ul style="list-style-type: none"> • 1-2 mg/kg IV (or IM if IV access cannot be easily gained) • 2nd dose after 30-60 minutes • Repeat (1 mg/kg IV) every 1-2 hours. Increase interval between doses once respiratory rate is <40-50 breaths/minute (e.g., to intervals of 4-6 hours)
Nitroglycerine – e.g., topical ointment (if available) or patches (e.g., 5 mg patch cut into quarters)	<ul style="list-style-type: none"> • Apply 0.25-0.5 cm ointment onto hairless, well perfused skin every 6 hours, for up to 3 days • ¼ patch applied to hairless skin once a day • Monitor blood pressure and discontinue if the patient becomes hypotensive
Butorphanol (anxiolytic effect)	<ul style="list-style-type: none"> • 0.2-0.3 mg/kg IM or IV
Mild or moderate heart failure; Chronic congestive heart failure (Stage C)	
Furosemide	<ul style="list-style-type: none"> • Dose range: 1 mg/kg SID/BID up to 3 mg/kg TID PO; monitor sleeping or resting respiratory rate and renal biochemistry/electrolytes after dose adjustments • Aim to give minimum effective dose to control CHF (with owner monitoring SRR at home)
ACE (angiotensin converting enzyme) inhibitor 1. Benazepril 2. Enalapril 3. Ramipril 4. Imidapril	<ol style="list-style-type: none"> 1. 0.25-0.5 mg/kg PO SID 2. 0.5 mg/kg PO SID 3. 0.125 mg/kg PO SID 4. 0.25 mg/kg PO SID
Telmisartan (angiotensin II receptor blocker)	1 mg/kg PO SID
Spirolactone (care with Maine Coon cats as risk of drug-induced facial dermatitis)	2 mg/kg PO SID
Pimobendan (care if suspected or known LVOTO)	0.1-0.25 mg/kg PO BID (e.g., 0.625 mg (½ tablet) or 1.25 mg (1 tablet) per cat PO BID
Refractory congestive heart failure (stage D)	
Torsemide	<ul style="list-style-type: none"> • 0.1-0.3 mg/kg PO SID/BID
Pimobendan (if not already used as above)	<ul style="list-style-type: none"> • 0.1-0.25 mg/kg PO BID. Consider TID administration
Hydrochlorothiazide (with amiloride in some preparations) (sequential nephron blockade)	<ul style="list-style-type: none"> • 1-2 mg/kg PO SID
Cardiogenic shock (Hypotension)	
Pimobendan (injectable or chewable tablets)	<ul style="list-style-type: none"> • 0.15 mg/kg IV • 0.625 mg (½ tablet) or 1.25 mg (1 tablet) per cat PO BID
Dobutamine	<ul style="list-style-type: none"> • 2-5 µg/kg/minute CRI
Tachyarrhythmias	
Atenolol (do not start if in uncontrolled CHF)	<ul style="list-style-type: none"> • 1 mg/kg PO SID/BID for ventricular or supraventricular arrhythmias
Diltiazem (modified release tablets)	<ul style="list-style-type: none"> • 1-3 mg/kg PO BID/TID for supraventricular arrhythmias
Sotalol	<ul style="list-style-type: none"> • 0.5-2 mg/kg PO BID for supraventricular or ventricular arrhythmias
Thromboembolism: treatment	
Methadone	<ul style="list-style-type: none"> • 0.1-0.3 mg/kg IV (q 6-8 hours)
Clopidogrel	<ul style="list-style-type: none"> • 18.75 mg per cat PO SID • Initial loading dose for FATE: 37.5 mg or 75 mg PO
Low molecular weight heparin (dalteparin)	<ul style="list-style-type: none"> • Initial dose 200 U/kg, then 100 U/kg SC BID
Rivaroxaban	<ul style="list-style-type: none"> • 1.25-2.5 mg PO per cat SID/BID (pending data in affected cats)
Apixaban	<ul style="list-style-type: none"> • 0.2 mg/kg PO SID (pending data in affected cats)
Aspirin	<ul style="list-style-type: none"> • 18.75 mg per cat PO every 3 days (or twice a week) (anti-platelet dose)
Alteplase (tissue plasminogen activator, tPA)	<ul style="list-style-type: none"> • 1 mg/kg IV
Cyproheptadine	<ul style="list-style-type: none"> • 0.1-0.5 mg/kg PO BID/TID
Thromboembolism: prevention	
Clopidogrel	<ul style="list-style-type: none"> • 18.75 mg per cat PO SID
Aspirin	<ul style="list-style-type: none"> • 18.75 mg per cat PO every 3 days (or twice a week) (anti-platelet dose)

Note that not all drugs may be licensed for cats and/or licensed for cardiomyopathy therapy

Backing off the furosemide dose and delaying the introduction of ACE-inhibitors should resolve this. In a cat with CHF who becomes azotemic, fluid therapy should be avoided, as this will increase preload and further decompensate the CHF. Instead, diuretics should be reduced or stopped for a short period while monitoring respiration.

●●●○ Cardiogenic shock

Cardiogenic shock may be seen in cats presenting with severe or end-stage cardiomyopathies, often in association with CHF. As a presentation, it is much less common when compared with CHF, but it may be precipitated by development of hemodynamically significant arrhythmias. It represents a major reduction in cardiac output and peripheral perfusion; owners report severe exercise intolerance and lethargy. On examination a cat is weak, with evidence of reduced perfusion; pallor, slow capillary refill, cold extremities and hypothermia. The cardinal sign is systemic hypotension (e.g., systolic blood pressure <100 mmHg). In CHF and its associated neuro-endocrine activation, including vasoconstrictors, all with the homeostatic priority of maintaining systemic blood pressure, it can be appreciated that hypotension is a grave prognostic indicator.

If cardiogenic shock is identified, as well as treating the CHF, positive inotropic support is indicated, preferably with pimobendan because of its inodilator effect. Dobutamine constant rate infusion (CRI) can also be used in the emergency setting, provided there is constant ECG and other monitoring available (Table 1).

●●●○ Feline Arterial Thromboembolism (FATE)

Cats with severe cardiomyopathies associated with LA dilatation and impaired LA function are at increased risk for formation of cardiac thrombi and subsequent systemic thromboembolism. This can be anywhere along the arterial tree, but typically distal aortic emboli result in severe pain, paralysis, loss of associated pulse (e.g., femoral artery), pallor (e.g., nail beds), and cold extremity of affected limbs. Muscles (e.g., gastrocnemius) are often contracted and painful on palpation. In some cases, acute presentation with thromboembolism can be the first sign of an underlying cardiomyopathy, and an important management goal in cardiomyopathy is to reduce the risk of FATE, especially if the LA is very dilated, reduced in function, or if any actual thrombus or spontaneous echocontrast (“smoke”) is evident on echocardiography. It is beyond the scope of this article to discuss FATE in depth, but strategies to treat or prevent it include one or more of the anti-thrombotic (anti-platelet) drugs (e.g., clopidogrel, aspirin) and/or anticoagulant drugs (e.g., dalteparin (low molecular weight heparin), rivaroxaban or apixaban (Table 1)). There does not appear to be any advantage (and there may

be increased risks) for using clot-busting drugs such as tissue plasminogen activator (tPA) [19]. Instead, conservative medication drives the cat’s own fibrinolysis system and prevents further platelet activation and aggregation. Cyproheptadine may reduce serotonin-mediated vasoconstriction of collateral vessels. Analgesia is imperative (usually opiates such as methadone). For prevention, clopidogrel is again indicated [20] (Table 1).

●●●○ Arrhythmias

Arrhythmias are common in feline myocardial disease and indicate a worse prognosis for survival [21]. Ventricular arrhythmias may arise because of increased wall stress, myocardial ischemia, or fibrosis which provides a substrate for re-entry arrhythmias. Atrioventricular blocks, including constant or paroxysmal complete atrioventricular block, may also reflect fibrosis. Atrial stretch may result in atrial [supraventricular] premature complexes or atrial fibrillation. Tachyarrhythmias will compromise diastolic function, with less time for diastolic filling, which leads to increasing filling pressures and decompensation into CHF. Antiarrhythmic therapy may be warranted in these cases (Table 1). Both brady- and tachyarrhythmias may impair cardiac output, leading to clinical signs such as lethargy or syncopal episodes. Malignant arrhythmias may result in sudden death, which may be the presenting sign in some cardiomyopathic cats.

●●●○ Classification of the other feline cardiomyopathies

Cats with most of the nhCMs (or end-stage HCM) will present with clinical signs described above and require to be managed for their presenting problem(s). However, the exact classification may be unimportant, as the presenting clinical problems must be addressed by treatment. The diagnosis of the actual underlying cardiomyopathy is typically based on echocardiographic phenotype, but classification of the specific non-hypertrophic cardiomyopathy (nhCM) is fraught with difficulties, and it is quite possible to have differing opinions given for the same cat and same images, although a recent consensus statement has provided useful guidance [1]. In particular, the diagnosis of end-stage HCM (where regression of left ventricular hypertrophy may reflect cardiomyocyte loss and fibrous replacement), restrictive cardiomyopathy and non-specific cardiomyopathy may differ between individual cardiologists. The echocardiographic diagnosis represents that point in time; unless the cat was evaluated earlier in its disease, it cannot be known whether the cat started off with HCM before becoming end-stage. A brief description of the criteria to diagnose a specific nhCM [2], with some representative echocardiographic images, is as follows.

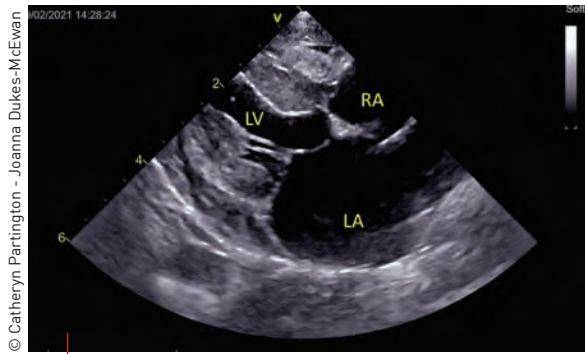


Figure 2. RPS long axis 4 chamber view showing end-stage HCM in a 13-year-old Domestic Shorthair cat. The diastolic LV wall thicknesses were 5.6-6.2 mm (≥ 6.0 mm confirms hypertrophy) and pericardial effusion is evident. This cat had atrial fibrillation.

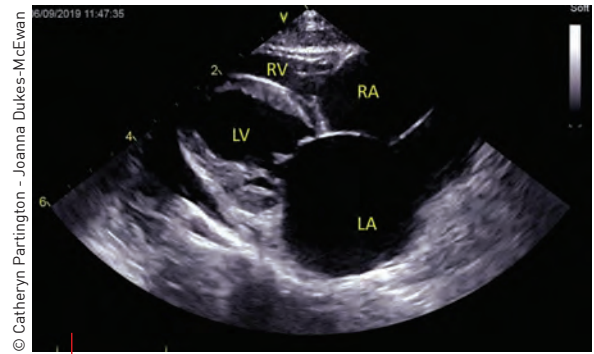


Figure 4. RPS 4 chamber long axis view of a Birman cat with the myocardial form of RCM. There is marked biatrial dilatation (especially the left atrium) but the left ventricular chamber measurements and wall thicknesses were unremarkable. Pleural effusion is present.

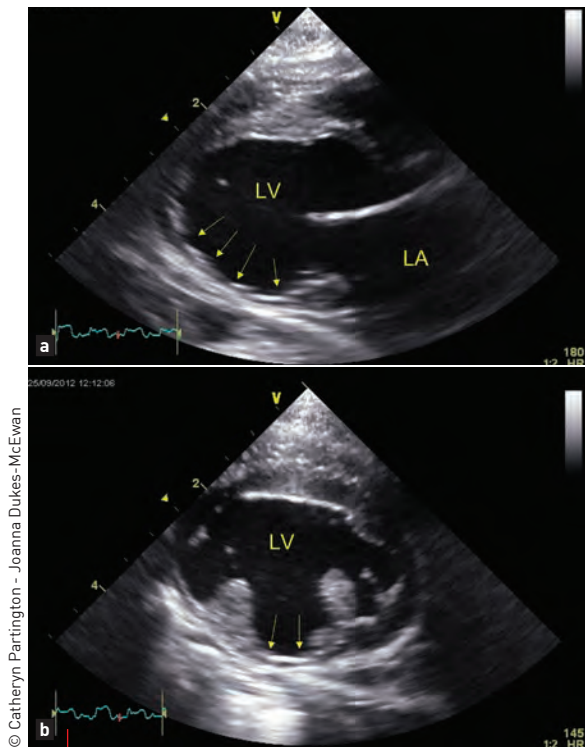


Figure 3. (a) RPS long axis 4 chamber view showing end-stage cardiomyopathy from a cat with presumed myocardial infarct and fibrous replacement, with regions of marked wall thinning and akinesis in the left ventricular free-wall (arrows). **(b)** RPS short axis view at the level of papillary muscles showing presumed myocardial infarct and fibrous replacement from the same cat as in **(3a)**. The thin LV wall (arrows) between the two papillary muscles can be seen.

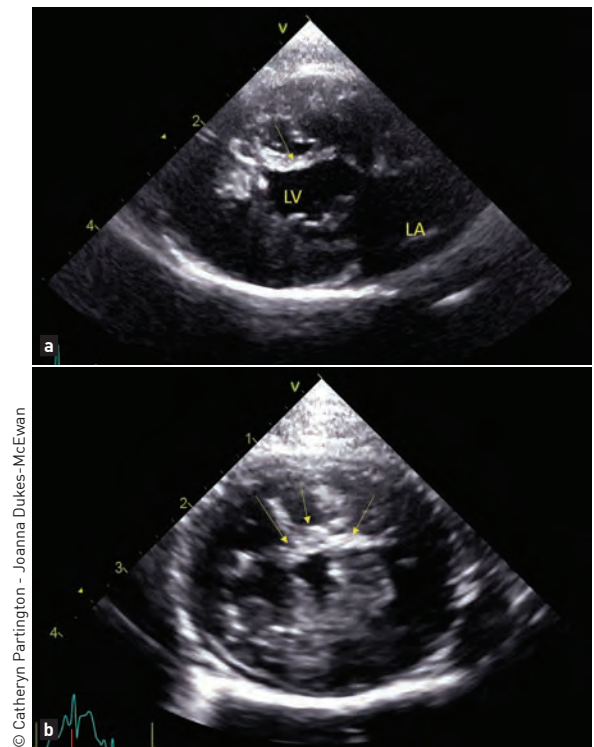


Figure 5. (a) RPS long axis 4 chamber view from a Siamese cat with the endomyocardial form of RCM. The endocardium is bright and irregularly thickened, and a bridging scar can be seen (arrow). **(b)** RPS short axis view at the level of the papillary muscles from the same Siamese cat as in **(5a)**. The echogenic bridging scar traverses the LV cavity (arrows).

Abbreviations used in Figures 3-8: A transmitral A (atrial contraction) wave (velocity), ARVC arrhythmogenic right ventricular cardiomyopathy, AV, atrioventricular, CHF congestive heart failure, DCM, dilated cardiomyopathy, E transmitral E (early) wave (velocity), FS fractional shortening, HCM hypertrophic cardiomyopathy, IVS interventricular septum, LA left atrium, LV left ventricle, LVFW left ventricular free wall, LVlDd left ventricular internal diameter in diastole, RA right atrium, RCM, restrictive cardiomyopathy, RV right ventricle, RVFW right ventricular free wall, RVOT, right ventricular outflow tract, PE pericardial effusion, Pl Eff pleural effusion.

1. **End-stage hypertrophic cardiomyopathy.** Although HCM is by far the most common cardiomyopathy, it may present in its end-stages with a different phenotype. This term is used if there was known prior HCM, even though there may be no segmental or generalized left ventricular hypertrophy, or the hypertrophy is very mild. The left ventricle may be hypokinetic or dilated (**Figure 2**) and myocardial infarction may be evident (**Figure 3**).

2. **Restrictive cardiomyopathy (RCM).** Non-hypertrophied, non-dilated and associated with left or biatrial dilatation (**Figure 4**) with diastolic dysfunction, RCM shows a restrictive filling pattern, characterized by transmitral E wave velocity being more than twice the A wave velocity. Note this form of diastolic dysfunction is not specific for RCM but can occur in any of the cardiomyopathies. It is subdivided into a myocardial form [22], where the endocardium is unremarkable (**Figure 4**), and an endomyocardial form [23,24], where

the endocardium can be irregularly thickened and echogenic, with bridging scars which may result in intra-ventricular obstruction (**Figure 5**). Siamese or oriental breeds may be predisposed.

3. **Non-specific cardiomyopathy** (previously called unclassified cardiomyopathy) [2]. Here the echocardiography features do not easily fit into the other cardiomyopathy criteria (e.g., systolic and diastolic dysfunction without left ventricular dilatation or increased hypertrophy) or there may be mixed features of other cardiomyopathies (**Figure 6**).

4. **Dilated cardiomyopathy (DCM)** [2]. Originally associated with taurine deficiency but now uncommon, but with a possible genetic or nutritional component (e.g., grain-free diets) when it occurs nowadays. Echocardiography can show a dilated left ventricle in systole (>12 mm) and diastole (>18 mm), and subjectively thin LV walls. The phenotype might also represent an end-stage of other cardiomyopathies (**Figure 7**).

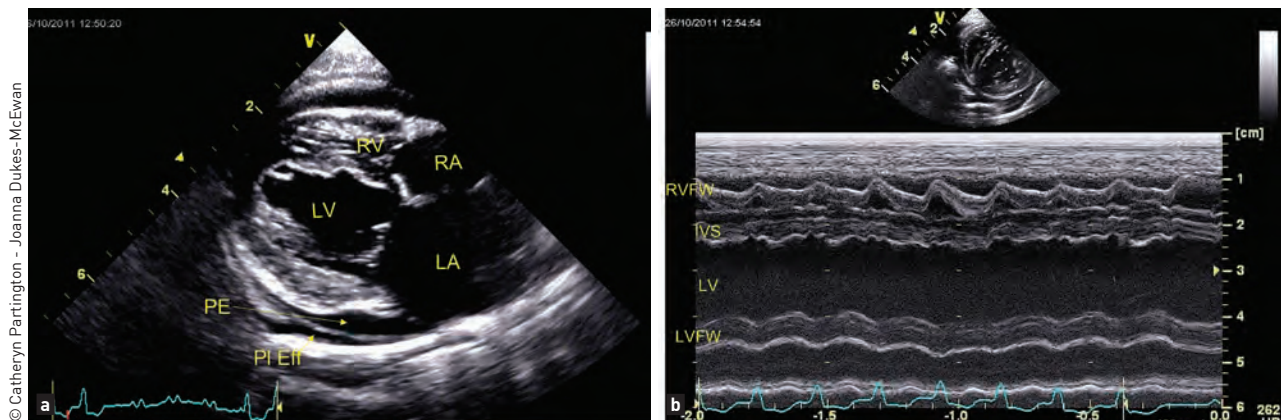


Figure 6. (a) RPS 4 chamber long axis view of a Domestic Shorthair cat diagnosed with unclassified (now non-specific) cardiomyopathy. The cat had a pericardial (PE) and pleural effusion (Pl Eff) with CHF. There was marked left atrial dilatation associated with diastolic dysfunction. The left ventricle was not particularly dilated, and LV wall thickness was within reference limits, but systolic function was impaired. (b) LV M-mode showing impaired LV systolic function in the same cat as in **Figure 6a**; the fractional shortening was low and right ventricular free wall motion is subjectively good.

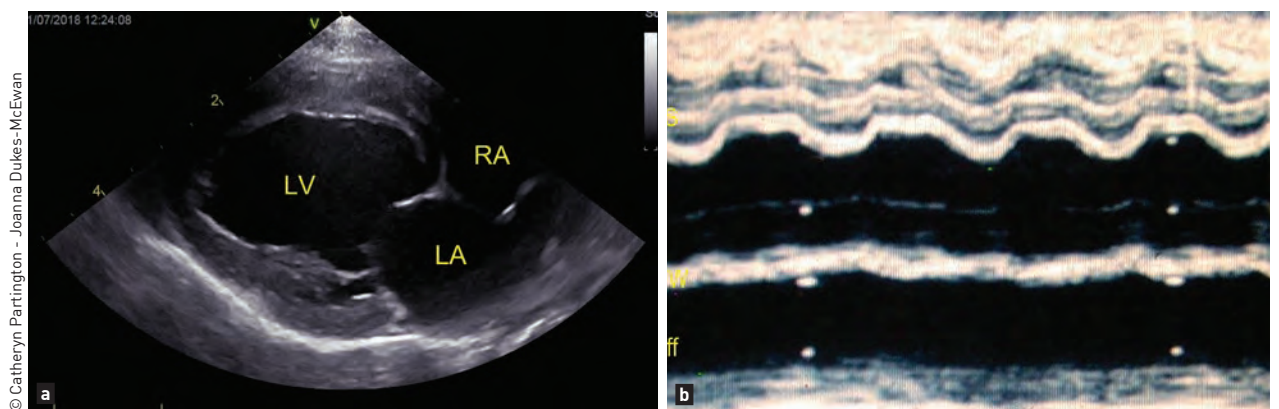
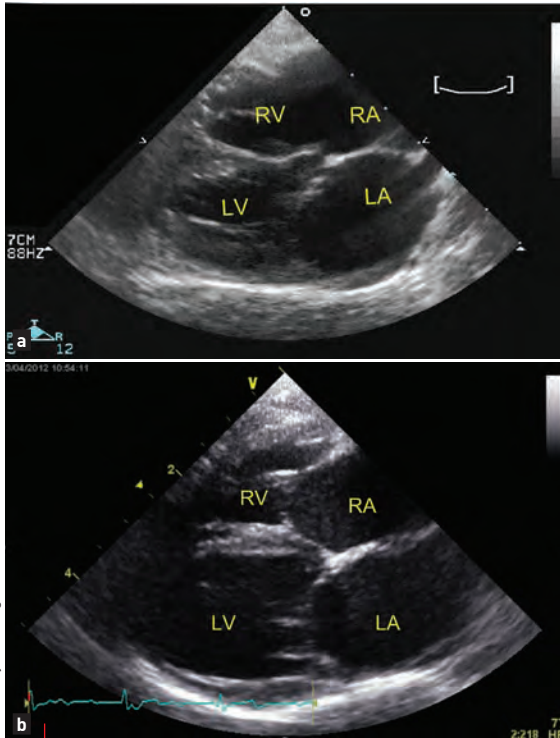


Figure 7. (a) RPS 4 chamber view from a Domestic Shorthair cat presenting with a DCM phenotype. The left ventricle is rounded, dilated and hypokinetic; the IVS appears thinner than the LVFW. This phenotype may represent an end-stage of another cardiomyopathy. (b) RPS M-mode directed from a short axis image at the tips of papillary muscle. This is from a Domestic Shorthair cat seen in 1989, which may have been an (unconfirmed) taurine-deficient DCM. The cat had severe CHF, including a pleural effusion.



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Figure 8. (a) Right parasternal long axis 4 chamber view from a Domestic Shorthair cat diagnosed with ARVC with right sided CHF (ascites, subcutaneous edema) and atrial fibrillation. The right side of the heart is dilated more than the left.

(b) Right parasternal long axis 4 chamber view from a Birman cat diagnosed with ARVC with biventricular CHF and 3rd degree AV block. All four chambers are dilated and the left ventricle was hypokinetic.

5. Arrhythmogenic right ventricular cardiomyopathy (ARVC) [25]. Cases typically present with predominantly R-CHF signs and a dilated right heart. However, left ventricular function is often impaired. It may be associated with ventricular or other arrhythmias. In contrast to dogs or humans with ARVC, complete atrioventricular block can occur. Birman cats are predisposed (**Figure 8**).



CONCLUSION

Classification of the different feline cardiomyopathies is fraught and there are no robust echocardiographic guidelines – the phenotype at the time of echocardiographic examination is described, but this may not be the original phenotype. However, the most important point is that the problem(s) identified at the clinical presentation should be addressed with treatment, and the therapeutic approach is similar regardless of the actual classification of the cardiomyopathy.

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FELINE SYSTEMIC HYPERTENSION



Alice M. Rădulescu

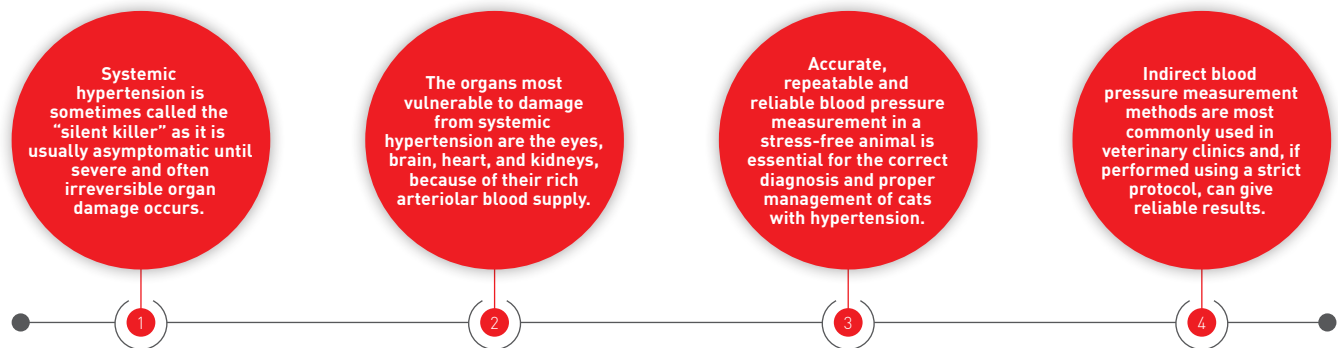
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Hypertension in the cat is now recognized as a significant contributor to ill health; Alice Rădulescu offers an overview of its underlying causes and the aids to diagnosis.

KEY POINTS



●○○○ Introduction

Systemic hypertension, which is defined as a persistent increase in systemic blood pressure, has become an increasingly common condition seen in veterinary practice today. This is mainly due to the growing awareness among veterinarians that hypertension is a disease that impacts both the lifespan and the quality of life of dogs and cats – although the increased incidence of systemic hypertension may also be a consequence of their improved life expectancy, as the frequency of diseases specific to old age, including hypertension, has increased. A significant contribution to this awareness has been the evolution in recent years of reliable devices for measuring blood pressure, which are now much more readily available to practitioners.

●●○○ Hypertension classification

Systemic hypertension can be caused by a number of factors:

- By environmental or situation-linked stressors – **situational** hypertension.
- In association with diseases that are known to induce high blood pressure – **secondary** hypertension.
- In the absence of other potentially causative disease processes – **idiopathic** hypertension.

Situational hypertension, also called “white coat” hypertension, is a transient increase in blood pressure from activation of the sympathetic branch of the autonomic nervous system due to arousal or anxiety. The “white coat” effect will typically increase systolic blood pressure by 15-20 mmHg (1), but greater increases (or even decreases) may

sometimes occur [2]. It is essential to be aware of this effect because the neurohormonal changes in a cat associated with the stress of a clinic visit can lead to a misdiagnosis of hypertension. However, this may not be easy to identify, because the effects of anxiety on blood pressure are unfortunately not predictable for individual animals.

Secondary hypertension, which is a persistent increase in blood pressure in animals suffering from other diseases known to cause hypertension, is the most diagnosed form in small animals. The most common conditions associated with systemic hypertension are kidney disease, endocrinopathies (hyperthyroidism, hyperadrenocorticism, diabetes, primary hyperaldosteronism), and pheochromocytoma. Secondary hypertension can also occur in animals that have received medication or ingested toxic substances that have a hypertensive effect, such as glucocorticoids, mineralocorticoids, erythropoiesis stimulants, phenylpropanolamine, cocaine, or methamphetamine.

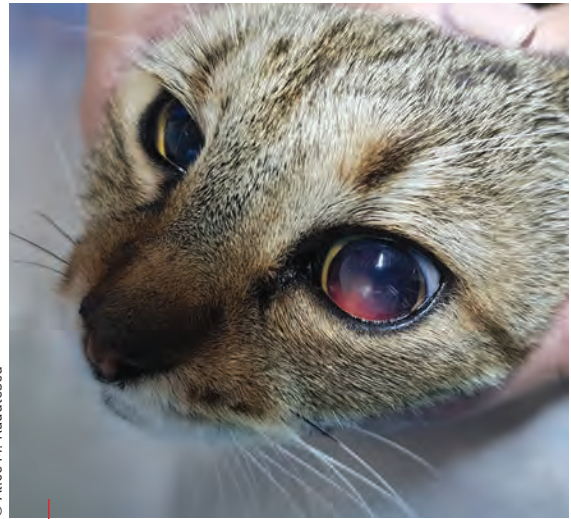
Idiopathic hypertension is a persistent pathological increase in blood pressure in the absence of any identifiable underlying cause. It is nowadays more frequently diagnosed than before, with recent studies showing an incidence of about 13-20% in cats [3-5].

There are differences in the onset, progression, and prognosis for the different types of hypertension. Secondary hypertension is found mainly in older cats (ten years plus) and associated with conditions specific to old age, such as chronic kidney disease, hyperthyroidism, and hyperaldosteronism. Once the underlying cause has been identified and treated, the hypertension may resolve. Primary (idiopathic) hypertension is much less commonly diagnosed in small animals, but can be found in cats of any age. Because there is no identifiable underlying disease, the aim here is to use medication to control the blood pressure and prevent damage to the target organs. In humans "white coat hypertension" is considered a risk



“Systemic hypertension is considered a disease of elderly animals, and therefore it is recommended to assess blood pressure as part of any routine screen in older pets.”

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Figure 1. Bleeding into the anterior chamber of the left eye in a cat with systemic hypertension (unilateral hyphema).

factor for subsequent hypertensive lesions, and the issue of its treatment has been raised. There is little evidence for this in animals, so there is currently no justification for treating feline situational hypertension.



Consequences and signs of hypertension

Also called the “silent killer”, systemic hypertension is often asymptomatic until severe organ damage occurs. The organs most vulnerable to systemic hypertension are the eyes, brain, heart, and kidneys, because of their rich arteriolar supply [6]. The damage is collectively referred to as **target organ damage (TOD)**.

TOD – eyes

Ocular damage syndrome in animals with systemic hypertension is called hypertensive choroidopathy and retinopathy [7]. In cats with high blood pressure, ocular lesions are frequently noted, with a reported prevalence between 68.1-100% in affected animals [4,8]. Signs that are easy for the owner to note, including hyphema (**Figure 1**) and fixed mydriatic pupils (**Figure 2**), are often the reason for presentation to the veterinarian. However, the most common lesion diagnosed is exudative retinal detachment, with an increased risk when systolic blood pressure exceeds 180 mmHg. Other lesions, such as retinal hemorrhage, multifocal retinal edema, retinal vessel tortuosity, retinal perivascular edema, papillary edema, vitreous hemorrhage, secondary glaucoma, and retinal degeneration have all been observed. Diagnosis of ocular damage requires an ophthalmic evaluation with funduscopic examination.

TOD – brain

Systemic hypertension can lead to brain damage from edema and hemorrhage, and is classified as hypertensive encephalopathy [9]. Neurological



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Figure 2. Severe mydriasis in a cat with systemic hypertension presented for sudden blindness due to bilateral retinal detachment.

signs associated with systemic hypertension have been reported both in cats [4,8] and dogs [10], although cats appear to be more prone. Hypertensive encephalopathy is more likely to occur with sudden increases in blood pressure, or where values are persistently greater than 180 mmHg. The clinical signs observed are typical of intracranial disease and can include altered mentation, vocalization, disorientation, ataxia, head tilt, nystagmus, torpor, convulsions, or even coma. Confirmation of brain damage requires neurological examination and specialist diagnostics such as magnetic resonance imaging.

TOD – kidneys

The kidneys are one of the preferred targets of systemic hypertension, but many affected animals also have concomitant chronic kidney disease, and it can be difficult to determine which condition came first. In the case of systemic hypertension, failure of the local blood pressure control system leads to increased intraglomerular capillary pressure, followed by proteinuria, which promotes the development of glomerulosclerosis, which in turn can exacerbate the initial hypertension [10]. Protocols for evaluating hypertensive renal patients

Table 1. IRIS subclassification of feline chronic kidney disease based on proteinuria status.

Proteinuric status	UPC ratio
Non-proteinuric	<0.2
Borderline proteinuric	0.2-0.4
Proteinuric	>0.4

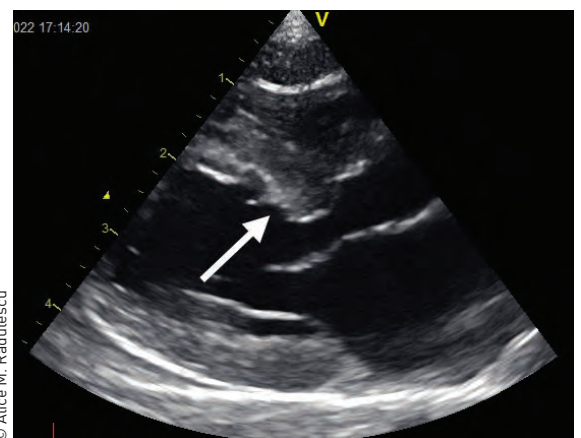
should include measurement of blood pressure, urine analysis, quantitative evaluation of proteinuria or albuminuria [11], measurement of serum SDMA and creatinine, radiography, and abdominal ultrasound. The IRIS (International Renal Interest Society) subclassification based on proteinuria using the Urine Protein:Creatinine ratio (UPC) (**Table 1**) may help determine whether antihypertensive therapy is indicated for individual cases.

TOD – heart

The heart is a target organ in both hypertensive cats [12] and dogs [13]. Chronic increases in afterload caused by systemic hypertension lead to compensatory myocardial hypertrophy in an attempt to normalize wall stress. Dogs are more likely to show diffuse and symmetric left ventricular concentric hypertrophy, proximal aortic bulb dilation, and aortic insufficiency, whilst cardiac changes detectable by echocardiography in affected cats include concentric hypertrophy of the left ventricular wall and interventricular septum, septal hypertrophy in the subaortic region (**Figure 3**), and dilation of the proximal aorta. At clinical examination any gallop sound, arrhythmia or murmur is strongly suggestive of heart damage, but additional tests such as thoracic radiography, electrocardiography and echocardiography are needed for confirmation.

When should BP be measured?

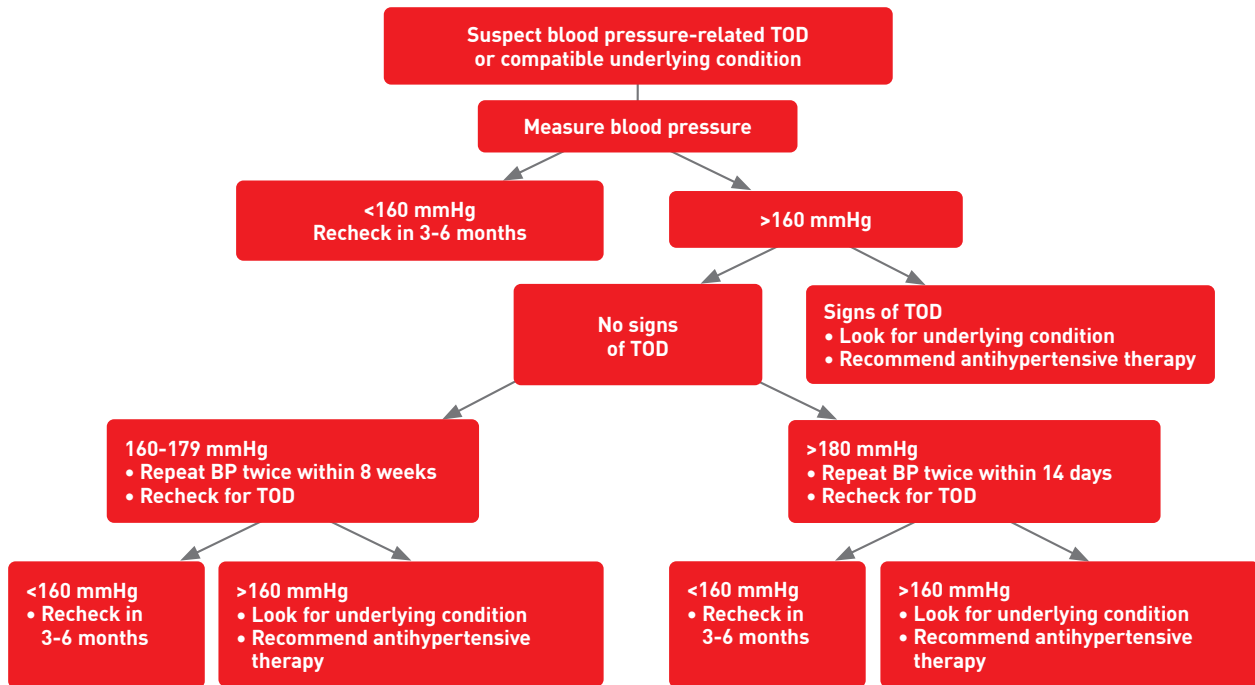
There are several situations in which it is recommended that blood pressure (BP) should be measured. Systemic hypertension is considered a disease of elderly animals, and therefore it is recommended to assess BP as part of any routine screen in older pets. A recent study found that the estimated incidence risk of systemic hypertension



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Figure 3. An ultrasound scan showing localized septal hypertrophy at the base of the interventricular septum in a cat with hyperthyroidism and systemic hypertension. This change may be seen also in normal older cats.

SYSTEMIC HYPERTENSION DIAGNOSTIC ALGORITHM



Box 1. A diagnostic algorithm for cats where there is target organ damage or evidence of an underlying condition that can cause systemic hypertension [15].

for cats older than nine years is 23.7% [14], so routine measurement should start at this point. Blood pressure should also be checked for any patient with evidence of a condition that is associated with hypertension, or when a drug that may cause secondary hypertension has been administered. In particular, blood pressure assessment should always be performed in cats with clinical manifestations compatible with target organ damage, and in this situation a single high value may be sufficient to confirm the diagnosis of systemic hypertension. **Box 1** shows an algorithm for decision-making when investigating a cat that shows signs of target organ damage that may be related to hypertension, or that has clinical signs suggestive of a condition which can cause systemic hypertension.

Animals with a suspected diagnosis of idiopathic hypertension should have their blood pressure measured several times to rule out situational hypertension, typically 5-7 times within the session and averaged. The first value obtained is usually ignored, as are individual readings which are much higher or lower than the majority of the results. If there is any doubt about the accuracy of the measurements, it is recommended to repeat the procedure after acclimatization or to reschedule for another day. In patients with conditions that can lead to systemic hypertension, regular blood pressure monitoring is advisable to detect any development over time; the author recommends doing this at eight-week intervals. This approach is also crucial for assessing the response to antihypertensive treatment.

BP measurement

Accurate, repeatable, and reliable blood pressure measurement is essential for the correct diagnosis and proper management of patients with hypertension, and a standardized staging system has been developed for the diagnosis of high blood pressure and the risk of developing target organ damage [15] (**Table 2**). Direct measurement by arterial catheterization is the gold standard for assessing blood pressure, but this is an invasive and impractical method for daily use in conscious patients, so indirect methods such as Doppler sphygmomanometry and high definition oscillometry (HDO) are commonly used in the veterinary clinic.

Direct measurement

Direct blood pressure measurement involves placing a catheter in an artery and connecting it to a pressure transducer, the most common

Table 2. ACVIM classification for risk categories for target organ damage (TOD) [15].

Risk category	SBP (mmHg)	TOD Risk
Normotensive	<140	Minimal
Prehypertensive	140-159	Low
Hypertensive	160-179	Moderate
Severely hypertensive	>180	High



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Figure 4. For direct measurement of blood pressure, a catheter is placed in a distal artery, usually the dorsal pedal artery.



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Figure 5. The arterial catheter must be securely bandaged once in place, and clearly labeled to avoid confusion with intravenous lines.

site for catheter placement in small animals being the dorsal pedal artery. After preparing the puncture site, palpate the pulse and insert the catheter in line with the vessel and at an angle of 45° (**Figure 4**). Pulsed and rapid blood flow through the catheter indicates successful placement in the artery. The catheter should then be fully advanced into the vessel and the stylus removed. Note that arterial catheters require a secure bandage to prevent dislodgement and bleeding, and should be clearly labeled (**Figure 5**) to avoid confusion with intravenous lines. Regular flushing of the arterial line is also required to ensure permeability and accuracy. The catheter is connected via a saline-filled tube to a pressure transducer placed at the same height as the heart. Once connected to the patient, the transducer must be calibrated to zero and then connected to a monitor; this will display a continuous pressure wave and numerical readouts of systolic (SAP), mean (MAP), and diastolic (DAP) blood pressures (**Figure 6**). From a clinical point of view, direct monitoring of arterial BP is indicated for animals in shock, hemodynamically unstable, at high anesthetic risk, severely hypertensive, requiring sympathomimetic support, or benefiting from mechanical ventilation [16]

Indirect measurement

Obtaining repeatable, reliable, and accurate blood pressure measurements by indirect methods is not easy, as several factors related to the device, patient, and operator can influence the results obtained. However, studies have shown a good correlation between direct and indirect methods, allowing practitioners to use the latter option, which is non-invasive, relatively inexpensive, and easy to perform.

Indirect measurement methods are based on detecting the return of pulsating blood flow after occlusion of the artery with an inflatable cuff. The choice of cuff is critical to ensure accurate readings; its width should be about 40% of the limb



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Figure 6. A monitor displays the readout as a continuous pressure wave, as well as systolic, mean and diastolic blood pressures.



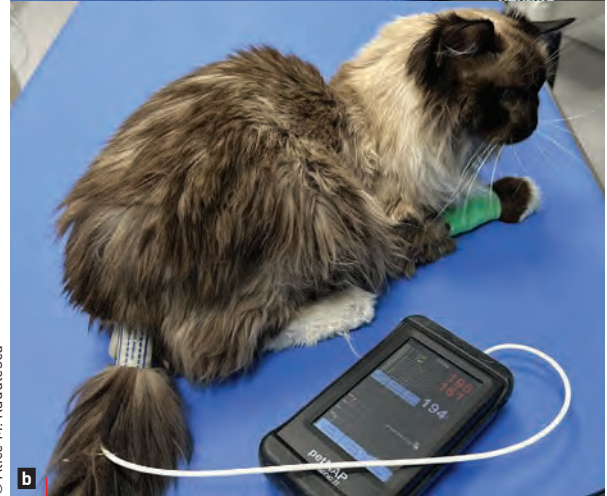
“It is essential to be aware of the ‘white coat’ effect because the neurohormonal changes in a cat associated with the stress of a clinic visit can lead to a misdiagnosis of hypertension.”

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Figure 7. Blood pressure measurement using the Doppler technique with placement of the transducer over the ulnar artery in the forelimb (a) and the dorsal pedal artery in the hindlimb (b).



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Figure 8. Blood pressure measurement with the high definition oscillometry (HDO) technique showing placement of the cuff at the level of the forelimb in the radial region (a) and at the base of the tail (b).

Table 3. A standard protocol for indirect blood pressure measurement [from 15].

- The chosen environment should be quiet, away from other animals, and with the owner present.
- The cat should not be sedated, but should be allowed to settle in the exam room for 5-10 minutes before starting to measure BP.
- The animal should be gently restrained and ideally in lateral recumbency, to limit the height difference between the heart base and the cuff.
- The cuff can be placed on the fore or hindlimb, or the tail.
- The cuff should be ~40% of the circumference of the limb or tail being used.
- Wherever possible the same person should perform all the measurements and should follow the agreed protocol.
- The cat should remain calm and as still as possible, and at least 5 consecutive readings should be taken, with the first result discarded.
- Repeat the procedure as many times as necessary, repositioning the cuff or changing the limb if required.
- An average of the results should be taken, with high and low extremes ignored; if results are doubtful, repeat the procedure as necessary.
- Results are recorded using a standardized format, noting the size of the cuff and the site used.
- The BP device should be checked and calibrated every six months.

circumference. If the cuff is too large, the values will be underestimated; if too small, the values will be overestimated [17]. Ideally the cuff should be positioned at the same level as the heart.

In order to obtain accurate blood pressure values, it is very important that measurement is done using a standard protocol (Table 3). This protocol must consider not only the practical aspects of the assessment and the type of device used, but also the environment in which the measurements are made, and how data collected are recorded. Blood pressure measurement should be common practice in veterinary clinics, but standardization is essential for practitioners to obtain meaningful results.

The **Doppler method** is currently recommended by most authors due to its speed and simplicity [18], and in addition the values obtained have good correlation with those from direct catheterization [19]. The technique detects arterial blood flow via an ultrasound transducer connected to an amplifier and a speaker or headphones. The probe is placed over a distal artery below the inflatable cuff which is connected to an aneroid manometer. The most common placement sites are on the palmar aspect of the metacarpal region (ulnar artery) or the

dorsal aspect of the metatarsal region (dorsal pedal artery) (**Figure 7**). Because detection of blood flow requires excellent contact between the probe and the skin, it may be necessary to first shave the chosen site and degrease the skin with alcohol. The inflatable cuff is positioned immediately above the prepared area and ultrasound gel is applied to the probe, which is then held using light pressure over the artery and parallel to the blood flow. Once blood flow is audible, the cuff should be inflated until the pulse can no longer be heard, and then deflated slowly while observing the manometer. The point at which the pulse first becomes audible is the systolic pressure value.

The **oscillometric method** is based on detecting oscillations (periodic fluctuations) inside the cuff produced by pulsations of the arterial wall. As the cuff is deflated, the oscillations increase rapidly, peak at MAP, and then rapidly decrease at DAP. The device screen will display SAP, MAP, DAP and pulse rate, usually alongside a graph of the detected oscillations which helps confirm the accuracy of the measurement. Most devices will typically measure MAP and employ programmed algorithms to calculate the SAP and DAP.

The technique is very simple, but the choice of cuff size, cuff placement, and animal position play a significant role in the accuracy of the results. The most common cuff placements are in the forelimb (using the radial artery), in the metatarsal region of the hindlimb (the caudal saphenous artery) or at the tail base (the coccygeal artery) (**Figure 8**).



CONCLUSION

The recommended approach for assessing a potential hypertensive cat involves reliable measurements of blood pressure and identifying possible target organ damage. Once a diagnosis of systemic hypertension has been established, further investigation should be performed to detect the underlying condition and establish appropriate treatment, which is beyond the scope of this paper; however, it is not enough simply to start a hypertensive cat on medication to lower its blood pressure without first determining the etiology wherever possible.



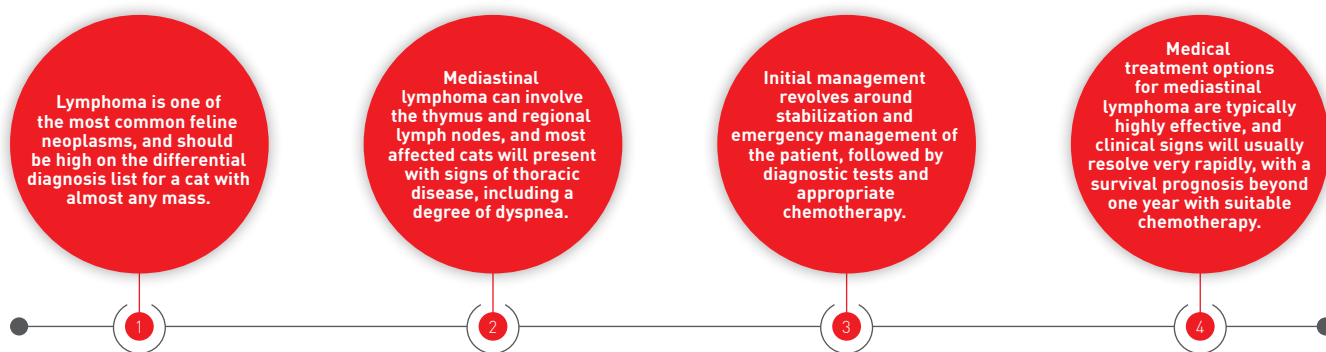
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FELINE MEDIASTINAL LYMPHOMA

Lymphoma is one of the most common neoplasms of cats, and the mediastinal form can be a major differential for a cat that presents with respiratory signs, as James Elliott describes.

KEY POINTS



Introduction

Lymphoma (historically often termed lymphosarcoma; LSA) represents a heterogeneous group of neoplasms that originate from lymphocytes. The neoplasms usually arise in lymphoid tissues such as lymph nodes, bone marrow and spleen, but they may develop in almost any tissue in the body due to the widespread distribution and migratory nature of lymphocytes. Lymphoma is one of the most common neoplasms seen in the cat and should be high on the differential diagnosis list for a cat with almost any mass.

Over time, a significant change in the epidemiology and clinical characteristics of lymphoma in cats has coincided with the integration of feline leukemia virus (FeLV) testing and elimination programs of the late 1970s and 1980s, and this was further modified by the appearance of FeLV vaccines in the late 1980s. The decline in FeLV-associated lymphoma mirrors the reduced incidence of FeLV infection. Interestingly, despite this, the overall prevalence of feline lymphoma is upwards; this seems to be mainly due to an increased frequency of the gastrointestinal form of lymphoma, as well as lymphoma in other anatomic sites (1).

The true incidence of feline lymphoma is unknown. There is no typical signalment for cats with lymphoma because it varies widely based on anatomic site and FeLV status. Siamese cats have

been suggested to be at increased risk of lymphoma, and may even develop distinctive subtypes of the disease with a unique biologic behavior (2).

Etiology of feline lymphoma

Viral factors

FeLV was historically the major cause of feline lymphoma, and most cases were associated with active infection. This often occurred in young cats, with a median age of around 3 years. In addition, there were certain anatomic subtypes heavily associated with FeLV infection, including the mediastinal form. However, given the dearth of FeLV these days, there has been a big shift in lymphoma cases, and this disease now affects significantly older cats, with a predominance in certain anatomic sites, such as gastrointestinal lymphoma.

FeLV is directly involved in lymphomagenesis, as it inserts into the cat's genome, resulting in cell proliferation and altered gene expression (1). Feline immunodeficiency virus (FIV) infection can increase the risk of lymphoma in cats, although here evidence suggests an indirect role, secondary to the immunosuppressive effects of the virus. FIV associated lymphoma is more likely to be of B-cell type, as opposed to the T-cell predominance associated with FeLV (3).



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Genetic and molecular factors

A predisposition of the oriental cat breeds to develop lymphoma suggests a potential heritable genetic predisposition (2).

Environmental factors

There is some data to suggest an increased risk of lymphoma in cats exposed to environmental tobacco smoke (ETS) (4).

Immunosuppression

As well as the increased risk of lymphoma in cats with the immunosuppressive FIV infection, there is also evidence that pet cats receiving cyclosporine following renal transplantation have an increased risk of cancer, including lymphoma (5).

Chronic inflammation

There is a suggested link between intestinal lymphoma and inflammatory bowel disease, and a potential association between *Helicobacter* infection and gastric mucosa-associated lymphoid tissue (MALT) lymphoma in cats, which is a recognized syndrome in humans. One study in cats found statistically significant increases in the prevalence of mucosa-invading bacteria and intravascular bacteria in large cell lymphoma biopsy samples (6). There is a suggestion that chronic inflammation from injection sites may increase the risk of developing subcutaneous lymphoma in cats (7).

●●● Mediastinal lymphoma – ○○ clinical signs

The mediastinal form can involve the thymus and regional (mediastinal, tracheobronchial and sternal) lymph nodes. Most cats present with signs of thoracic disease, due either to the space-occupying effect of the tumor, or secondary to pleural effusion, which is very common. The clinical signs associated with mediastinal lymphoma include dyspnea (80%), tachypnea, and a non-compressible cranial thorax with dull heart and lung sounds. Horner's syndrome and cranial vena cava (caval) syndrome may be seen, with associated swelling of the head and neck due to compression of vessels draining the head. However, in the author's experience caval syndrome is very

uncommon in cats with mediastinal lymphoma, and much more common in canine mediastinal lymphoma/thymoma. Hypercalcemia occurs frequently with mediastinal lymphoma in dogs, but is actually very rare in cats.

Most patients present with some degree of dyspnea, and initial management revolves around stabilization and emergency management until they are comfortable enough to undergo diagnostics. This can involve oxygen supplementation with minimal handling to reduce stress, and sedation or analgesia [e.g., butorphanol] if indicated. There should be rapid assessment to verify if pleural effusion is present [ultrasonography, radiography]; if there is a large volume of fluid this must be drained quickly, as it contributes significantly to the dyspnea.

The disease is confined to the mediastinum in most cases, although there can certainly be involvement of other regional nodal groups or distant sites. The author has commonly seen involvement of prescapular or even mandibular lymph nodes, particularly later in the disease course, often at the time of relapse. The author has also seen a few cases that initially present with a large mass that has appeared suddenly in the prescapular region. This has ultimately been demonstrated by computed tomography (CT) to be contiguous with a large mediastinal mass, as opposed to actually being the prescapular lymph node.

The majority of cats with mediastinal lymphoma in older reports were young (median age, 2-4 years), FeLV positive, and had a T-cell immunophenotype tumor. However, as expected with the decline of FeLV, the typical phenotype has altered. In a recent UK study of 55 cats with mediastinal lymphoma, the majority (>90%) were antigenically FeLV/FIV negative, young (median age, 3 years), male (3.2:1 male-to-female ratio), and nearly one-third were of the Siamese breed (8). Immunophenotype was not reported, probably as it is performed less in cats. This is likely because most studies suggest that, unlike in dogs, immunophenotype appears to have less prognostic significance in cats.

A form of mediastinal lymphoma also occurs primarily in young, FeLV-negative Siamese cats that appears to be less biologically aggressive and more responsive to chemotherapy than FeLV-associated forms.

●●● Mediastinal lymphoma – diagnostics

Thoracic radiographs may identify an obvious mediastinal mass (**Figure 1**), although sometimes the presence of significant pleural effusion can make it difficult or impossible to visualize prior to drainage (**Figure 2**) and repeat radiographs or ultrasound may be necessary (**Figure 3**). CT may be helpful, as a mass can be seen irrespective of the presence of effusion; however, this imaging modality generally does not contribute to a definitive diagnosis, because there are several differentials for a cat with a mediastinal mass.

Fine-needle aspirate (FNA) cytology of the mass or cytologic evaluation of pleural fluid may be sufficient to establish a diagnosis. In most cats, lymphoma exfoliates well with a fine-needle aspiration, and the finding of a monomorphic population of intermediate or large lymphoid cells will confirm the diagnosis (**Figure 4**). On occasion, a definitive diagnosis of lymphoma in cats with a mediastinal mass can be more challenging.

A major differential for mediastinal lymphoma is thymoma. The cytologic features of thymoma can be distinct from lymphoma in many cases, but the diagnosis can be challenging because of a preponderance of small lymphocytes in thymoma. Mast cells can also be seen in up to 50% of aspirates from thymomas (**Figure 5**). The addition of immunophenotypic and clonality assessment may be helpful in equivocal cases.

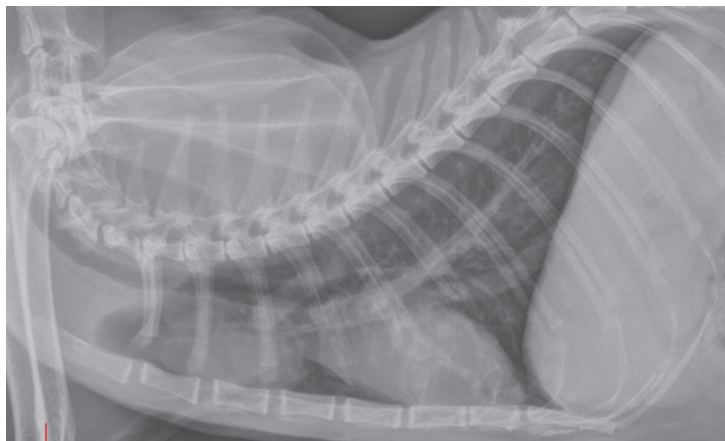
Where the diagnosis is equivocal, potential additional diagnostics could include:

- **Flow cytometry:** this is where a FNA of the mass or a sample of pleural fluid containing cancer cells (transported in a special medium provided by the laboratory) is analyzed by a flow cytometer. Based on the cell size, complexity and labelling



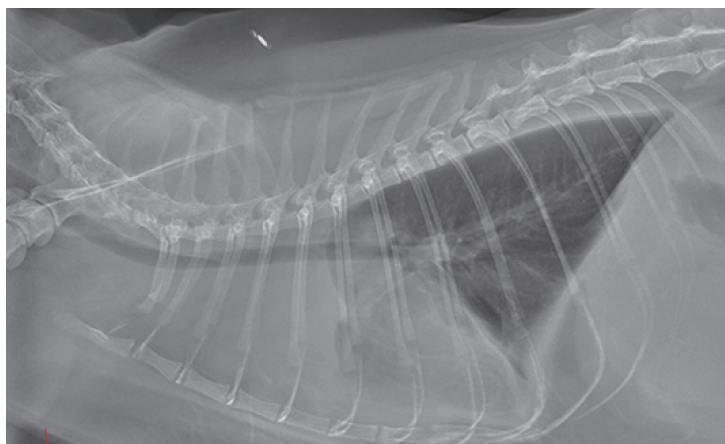
“In most cats, lymphoma exfoliates well with a fine-needle aspiration, and the finding of a monomorphic population of intermediate or large lymphoid cells will confirm a diagnosis.”

James Elliott



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Figure 1. A lateral thoracic radiograph of a cat; note the ovoid soft tissue mass overlying sternbrae 2-4, cranial to the heart. This was cytologically confirmed to be lymphoma.



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Figure 2. A lateral thoracic radiograph of a cat showing a moderate volume of pleural effusion. Note the scalloped lung edges due to pleural fluid and the lack of detail in the cranial mediastinum, as well as the loss of the cardiac outline. Post-drainage, a cranial mediastinal mass was visible. In this case, the mass did not require sampling, as cytology of the pleural fluid was consistent with large cell lymphoma.



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Figure 3. A thoracic ultrasound scan from the cat in **Figure 2**. After drainage, breathing was significantly improved, and a hypoechoic mass could be visualized.

for specific cell-surface markers, lymphoma and the phenotype (B or T) can be diagnosed. Although well established in dogs, the technique is less common in cats, and certain laboratories may not currently recommend this test for cats.

- **PARR analysis (PCR for Antigen-Receptor Re-arrangements):** this is where DNA is extracted from cells on cytology slides or biopsy specimens (even if already stained and dried or formalin-fixed) and analyzed. Most lymphomas arise from either B or T lymphocytes, and the cells will all be clones of each other. Therefore, this test tries to establish if the cells analyzed all have genetically identical B or T-cell receptors (and are therefore cancerous) or whether they are genetically diverse (*i.e.*, not cancer, such as an inflammatory population of lymphocytes)

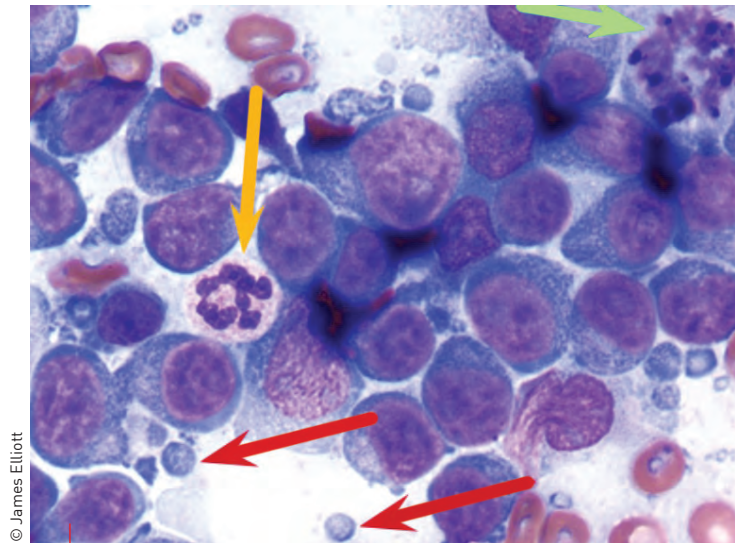
Finally, Tru-Cut biopsy can be useful for large masses which communicate with the chest wall (to ensure there is a low risk of causing iatrogenic pneumothorax), but in the author's practice this option is rarely required nowadays.

●●● Treatment options and prognosis

Chemotherapy is by far the most utilized treatment option for cats with mediastinal lymphoma. Generally, lymphoma is considered a systemic disease, even if it appears to be localized at diagnosis. This means that although a cat with localized lymphoma (*e.g.*, mediastinal lymphoma) might appear disease-free in other anatomic sites based on imaging (or even cytology, *e.g.*, of the liver or spleen), it is considered likely that they will have cancer cells in these locations at a microscopic level. Therefore, the goal of cytotoxic chemotherapy is to treat both the known macroscopic disease, but also any occult, microscopic disease.

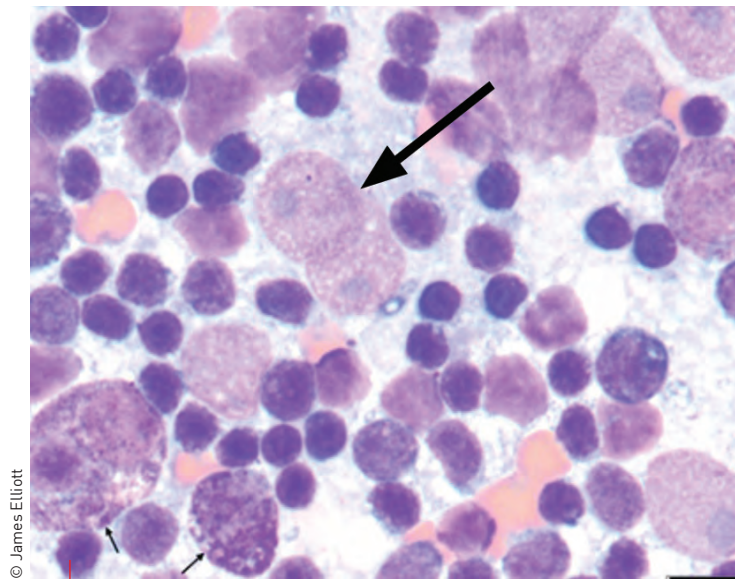
Surgery is not indicated in cats with mediastinal lymphoma, for the reasons outlined above and the morbidity and risk associated with thoracic surgery. Wound healing would also delay the instigation of chemotherapy. In addition, medical treatment options are typically (at least initially) highly effective, and lymphoma responds very rapidly. Therefore, whilst pets with some tumor types will rapidly improve clinically with surgical removal, this is not the case in mediastinal lymphoma.

Most cats with lymphoma at any site, including mediastinal, will be offered either a COP (cyclophosphamide, vincristine (oncovin) and prednisolone/prednisone) or CHOP (COP plus doxorubicin (hydroxydaunorubicin)) protocol, as shown in **Tables 1 and 2**. CHOP-type protocols are the standard of care in humans with the most common types of lymphoma. Similarly, canine lymphoma (particularly of the B-cell



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Figure 4. Cytology from a cytospin preparation of pleural fluid from the cat in **Figures 2 and 3**. Note the monomorphic population of very large, round cells with features of immature lymphoblasts, and the intense blue cytoplasm, coarse open chromatin with multiple nucleoli and perinuclear clear zone. Also note the solitary eosinophil (yellow arrow), mitotic figures (green arrow) and lymphoglandular bodies (red arrows).



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Figure 5. Cytology from a fine-needle aspirate of a mediastinal mass in a cat which was ultimately surgically removed and shown to be a thymoma. The predominant cell population is small, mature lymphocytes with a thin rim of cytoplasm and dark, condensed purple nuclei. In addition, there are scattered epithelial cells (long black arrow) and two mast cells (short black arrows). This is a classic cytology for thymoma, with a predominance of small mature lymphocytes admixed with epithelial cells and mast cells. This is in contrast to lymphoma, where a monomorphic population of large, immature lymphocytes are seen, as in **Figure 4**.

type) is typically treated first-line with a CHOP (*i.e.*, doxorubicin-inclusive) protocol by most oncologists. The best option for feline lymphoma at any site is less clear-cut, and both COP and CHOP protocols are widely utilized, with most studies failing to demonstrate that CHOP is significantly superior to COP. In addition, doxorubicin appears to be less effective as a single agent in cats compared to dogs, and nephrotoxicity is a possible adverse effect in cats. Given the propensity for chronic kidney disease in ageing cats, this must be considered when making a therapeutic plan. Doxorubicin is also an extreme vesicant, causing potentially extensive tissue sloughing in the event of extravasation, so feline patients may require sedation for safe administration, depending on temperament. Doxorubicin is, however, very unlikely to cause cardiotoxicity in cats at standard doses and schedules.

A retrospective study of cats with mediastinal lymphoma treated with either COP or CHOP protocols demonstrated an overall response rate of 95%, with an overall median survival time (MST) of just over a year (and 980 days if complete response is achieved) [8]. Complete response (CR) and partial response (PR) rates did not differ significantly between COP and CHOP protocols, with overall median survival reported as 373 days (range 20-2015 days). Cats achieving CR survived longer

(median 980 days vs. 42 days for PR). Age, breed, sex, location (mediastinal vs mediastinal plus other sites), viral status and steroid pre-treatment did not affect response or survival. The prevalence of FeLV positive cats in this study was low (9%), with males and young Siamese cats appearing to be over-represented.

In contrast, mediastinal lymphoma in young FeLV-positive cats is generally associated with a poor prognosis, and MSTs of approximately 2 to 3 months can be expected after treatment with either CHOP or COP protocols. Slightly more promising results were obtained in a recent, small retrospective Brazilian study, where cats with mediastinal lymphoma (from a 90% FeLV positive population) had a MST of approximately 7 months using a novel protocol consisting of vincristine, prednisolone, doxorubicin and lomustine [9].

Chemotherapy should not be thought of as a “formula”, and whilst protocols are useful as a starting point, they should be modified for the individual. Adverse effects can include gastrointestinal upset, myelosuppression (principally neutropenia) and – rarely – drug-specific toxicity such as doxorubicin-induced renal injury. An awareness of the patient’s history, previous response to chemotherapy and any adverse effects, and appropriate blood tests are required in an effort

Table 1. A standard COP (cyclophosphamide, vincristine (oncovin) and prednisolone/prednisone) protocol for cats.

Drug	Week 1	Week 2	Week 3	Week 4	Weeks 7,10,13,16,19,22,25
Vincristine	x	x	x	x	x
Cyclophosphamide	x			x	x
Prednisolone	x	x	x	x	x

Providing the patient is in remission at week 25, chemotherapy (including prednisolone) is ceased. If complete remission has not been achieved by week 7 (*i.e.*, after the more intense induction period of weeks 1-4), additional or alternative therapies should be considered. Historically, continuous COP-based chemotherapy schedules have been recommended. In the author’s experience, cats in remission after 6 months of therapy can be treated with discontinuous schedules as above.

Vincristine: 0.7 mg/m² IV; **Cyclophosphamide:** 250 mg/m² IV/PO; **Prednisolone:** 2 mg/kg PO q24h for 14 days then 1 mg/kg q48h

Table 2. A standard CHOP (COP plus doxorubicin (hydroxydaunorubicin)) protocol for cats.

Week	1	2	3	4	6	7	8	9
Vincristine	x		x		x		x	
Cyclophosphamide		x				x		
Doxorubicin (or epirubicin)				x				x
Prednisolone	x	x	x	x	x	x	x	x
Week	11	13	15	17	19	21	23	25
Vincristine	x		x		x		x	
Cyclophosphamide		x				x		
Doxorubicin (or epirubicin)				x				x
Prednisolone	x	x	x	x	x	x	x	x

Vincristine: 0.7 mg/m² IV; **Cyclophosphamide:** 250 mg/m² IV/PO; **Doxorubicin or epirubicin:** 1 mg/kg or 25 mg/m² IV; **Prednisolone:** 2 mg/kg/day, week 1; 1.5 mg/kg/day week 2; 1.0 mg/kg/day week 3; thereafter 0.5 mg/kg/day PO



Figure 6. Cats can enjoy an excellent quality of life whilst receiving chemotherapy.

to maintain the optimum dose intensity – *i.e.*, in deciding whether the chemotherapy dose should be increased, reduced or maintained. Most clinicians will proceed with chemotherapy providing the absolute neutrophil count (not the total white cell count!) is greater than $2.5 \times 10^9/L$, but it may be safe to proceed if the count is lower than this, depending on various factors. There is really no definitive point at which the neutrophil count suggests that it is safe to continue with a given protocol, and different clinicians will have different experiences, and some clinicians may have different cut-offs for different drugs. For example, doxorubicin is a particularly myelosuppressive drug which can cause severe neutropenia, so if used some oncologists will have a higher “threshold” for the neutrophil count before happily proceeding with the next dose. Equally, some clinicians may be more cautious if they are treating a frail patient, if they have experienced severe neutropenia previously, or if the pet owner has major concerns regarding possible adverse effects. Conversely, if there is no neutropenia/myelosuppression at all and no clinical adverse effects, some clinicians may consider a dose increase for subsequent treatments of the chosen drug. A recent study showed that in dogs receiving a 19-week CHOP protocol for lymphoma, treatment proceeded as long as the neutrophil count was $>1.5 \times 10^9/L$; this reduced the number of dose delays and did not result in a significant increase in adverse effects. Whilst such data is not currently published for cats, it is likely that a “safe” threshold for chemotherapy may be less than $2.5 \times 10^9/L$, but a significant neutropenia may require drug dose reduction or increased dosing interval. So if a cat’s neutrophil count is below the chosen cut-off when a dose is due, a 2-7 day delay (depending on the magnitude of the neutropenia) should be instituted. If this continues for future doses or the neutropenia is severe, then a dose reduction may be warranted for future doses.

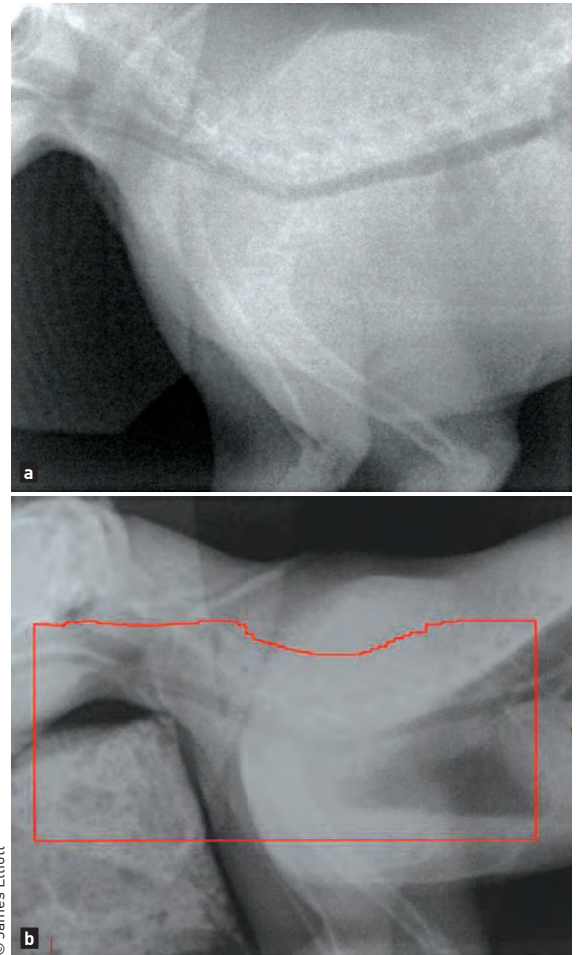


Figure 7. “Port film” radiographs taken of a cat with mediastinal lymphoma being treated with palliative-intent radiotherapy, which had previously responded to CHOP chemotherapy, but had relapsed in the mediastinum and mandibular/prescapular nodes a few months later. There was no response to re-introduction of chemotherapy. The pre-treatment radiograph (a) shows the absence of cardiac silhouette and pleural effusion. By the final treatment, only 4 days later (b), there was a complete radiographic response to treatment. The red line denotes the area that was treated with radiotherapy.

This exemplifies the “art” of chemotherapy, which comes partly with experience but also over time treating the individual patient, and indeed most cats tolerate chemotherapy well. So with appropriate experience and skill, drug or dose modifications, dose reductions or holidays, drug frequency alterations and anti-emetic prophylaxis, cats can enjoy an excellent quality of life whilst receiving chemotherapy. Of note, cats appear resistant to cyclophosphamide-induced cystitis and doxorubicin-induced cardiotoxicity, and they rarely become septic even with severe drug-induced neutropenia. Multiple studies report that the majority of owners are happy with their pet’s quality of life whilst receiving chemotherapy for lymphoma (10) (**Figure 6**).

Where clinical signs reappear, various rescue chemotherapy protocols are available, utilizing different drugs to which the tumor cells have not yet been exposed (**Table 3**). Unfortunately, there is often intrinsic chemoresistance or acquired cross-resistance to many of these drugs. Many cats are very symptomatic when they relapse, which may allow less time to try various rescue protocols in order to determine the most effective regime. Response rates are usually modest and typically not durable, although in pets that do develop a strong partial or complete response, outcome is significantly improved.

Radiotherapy has been commonly used very successfully for certain types of solitary feline lymphoma, particularly nasal lymphoma, yet interestingly it has seldom been used for mediastinal lymphoma. The reasons for this are probably multifactorial, including the previous association with FeLV and a poor prognosis, the scarcity of available treatment centers, potentially poor (repeated) anesthetic candidacy, difficulty in tumor targeting due to respiratory motion, large volumes of pleural effusion, large tumors and the perceived radiation sensitivity of normal intrathoracic tissues near the tumor (particularly the pericardium, heart and lungs). Lymphocytes are exquisitely sensitive to radiation and die very quickly, and lower doses are often required to effectively treat lymphoma than most other tumor types. Therefore, with the advent of more sophisticated radiation facilities, this therapy may become a potential treatment resource. For example, patients with mediastinal lymphoma often relapse in the mediastinum, so radiotherapy alone, or in combination with chemotherapy, may more effectively eradicate neoplastic lymphocytes than chemotherapy alone, and could become part of definitive-intent, first-line treatment. To date, the author has mainly used radiotherapy as a palliative-intent treatment for relapsed cases following initial treatment with systemic chemotherapy, with good (albeit temporary) results (**Figure 7**).

Table 3. Common “rescue” chemotherapy protocols for recurrence of feline lymphoma.

Drug(s)	Typical response rate	Median remission time
Lomustine, methotrexate and cytarabine	46%	61 days
MOPP (mechlorethamine, vincristine, procarbazine, prednisolone)	70%	166 days
MOMP (mechlorethamine, vincristine, melphalan, prednisolone)	58%	39 days
DMAC (dexamethasone, melphalan, actinomycin D, cytarabine)	26%	14 days
Lomustine (CCNU)	54%	39 days



CONCLUSION

Cats with mediastinal lymphoma mostly present with relatively acute-onset respiratory signs and often require emergency triage and management, although a diagnosis is relatively easily achieved. These days, cats with mediastinal lymphoma are usually FeLV negative and can have a survival prognosis of over a year with suitable chemotherapy. In cats achieving a complete remission, duration of remission can be very durable (>2.5 years). A subset of younger, male, FeLV negative oriental cats can have a particularly good prognosis, but most cats will respond favorably to chemotherapy and can have a good quality of life on treatment.



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