Feline Cardiomyopathies

Reference Notes

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Overview

Cardiomyopathies are heart muscle diseases not caused by malformations, valvular diseases, high blood pressure, or coronary abnormalities. Genetic and idiopathic myocardial diseases are termed *primary* cardiomyopathies. These include the ventricular *phenotypes* of hypertrophic, dilated, restrictive, right ventricular, and nonspecific cardiomyopathies. Of these conditions, hypertrophic cardiomyopathy (**HCM**) phenotype is most common and important. Cats are occasionally diagnosed with myocarditis and a poorly defined disorder called "transient myocardial thickening." Myocardial infarction is also observed in cats, but it is typically associated either with HCM another form of myocardial disease.

These myocardial phenotypes are believed to develop in most cases as genetically predetermined, adult-onset disorders; essentially sarcomeric heart diseases of mono- or polygenetic basis. However, the precise etiology of most feline cardiomyopathies has not yet been elucidated in terms of genetic abnormalities and therefore many cases are considered "idiopathic". Similar phenotypes of cardiomyopathy can develop *secondary* to other diseases, including systemic hypertension, hyperthyroidism, taurine deficiency, diabetes mellitus, growth hormone excess (acromegaly) and high-output states such as moderate to severe anemia (see last section of these notes for more details). Inasmuch as the echocardiographic findings overlap between primary and secondary myocardial diseases, these conditions should be distinguished whenever possible, because patient management and long-term prognoses can differ.

Other Types of Feline Heart Disease (in brief) The diagnosis of primary *pericardial disease* in cats is comparably rare. Peritoneopericardial diaphragmatic hernia is encountered regularly as a congenital defect and is often undiscovered until a cat is mature. Most pericardial effusions in cats occur secondary to congestive heart failure and can be an early sign of impending failure on an echocardiogram. Infectious causes - including bacterial and viral (FIP) diseases - and cardiac lymphoma are uncommon reasons for primary pericardial effusion in cats.

Acquired *valvular heart diseases* are also uncommon except those associated with feline cardiomyopathies. Infective endocarditis is very rare; degenerative valve disease is occasionally encountered especially in older cats. The mitral valve can also change its length or thickness in association with feline hypertrophic cardiomyopathy. In younger cats with murmurs, congenital valve malformations (and shunts) also must be considered.

Primary *cardiac arrhythmias* in cats do occur, but most cases of persistent atrial or ventricular

ectopy are associated with a myocardial disorder. Metabolic disorders, especially those of potassium, can result in transient cardiac arrhythmias in cats. Atrioventricular (**AV**) blocks are underdiagnosed in older cats. Cats with complete AV block frequently have stable escape rates of between 110 and 130 per minute, which can cause the bradyarrhythmia to be overlooked.

Some cats with AV block do develop congestive heart failure (**CHF**) with jugular distention and pleural effusions; others do not exhibit cardiac signs unless transient periods of cardiac arrest (from unstable escape foci) lead to syncope (that is usually misdiagnosed as a seizure).

There are five main *vascular diseases* to consider in cats. Coronary arterial narrowing and thrombosis is usually associated with feline HCM or restrictive cardiomyopathy (**RCM**). Nearly every case of arterial thromboembolism (**ATE**) is related to one form or another of cardiomyopathy. Uncommon to rare causes of ATE include pulmonary carcinoma and infective endocarditis.

Systemic hypertension can cause secondary left ventricular hypertrophy that is typically mild. These cats can have cardiac signs such as a murmur or gallop sound but often present for other target organ damage, especially retinal injury.

Pulmonary hypertension is rarely due to heart failure or heart disease in cats aside from congenital shunts or severe pulmonary parenchymal disease or heartworm infection.

Abbreviations Used
2DE – two-dimensional echocardiography
ACE – angiotensin converting enzyme
AF – atrial fibrillation
ATE – arterial thromboembolism
cTnI – cardiac troponin-I (inhibitory)
NT-proBNP – Nitrogen terminal of the prohormone of B-type natriuretic peptide
CHF – Congestive heart failure
DCM – dilated cardiomyopathy
EF – ejection fraction (stroke volume/end-diastolic volume)
LA – left atrium/atrial
LA/Ao – ratio of LA to aortic dimension
LV – left ventricle/ventricular
LVOT(O) – left ventricular outflow tract (obstruction)
MR – mitral regurgitation
NCM – nonspecific cardiomyopathy
RA – right atrium/atrial
RAAS – renin-angiotensin-aldosterone system
RCM – restrictive cardiomyopathy
RV – right ventricle/ventricular
SAM – systolic anterior motion of the mitral valve
TR – tricuspid regurgitation

Idiopathic aortic dilatation (aortoannular ectasia) is often observed in middle-aged and older cats. Whether or not aortic stiffness is altered in this disease, or whether this vascular change contributes to systolic hypertension, or stimulates hypertrophy in the dorsal ventricular septum has not been studied (aortic dilation can also be associated with systemic hypertension, so that should be excluded). This proximal aortic lesion is frequently associated with an abnormal septal to aortic angle and with discrete upper septal thickening (DUST), also called discrete interventricular septal thickening (DISH). In most cases this seems isolated and benign, although some cats with HCM will demonstrate prominent dorsal septal bulges as part of their more generalized disease.

Hypertrophic Cardiomyopathy

This presentation focuses mainly on HCM, but complications of other myocardial disease are similar and, in most cases, *managed as per HCM*. Details of this disease have been detailed in a special issue of the Journal of Veterinary Cardiology[1] and in a more recent ACVIM Consensus Statement[2] and comprehensive review[3].

Feline HCM is characterized by thickening of the LV due to myocyte hypertrophy. The RV can be mildly thickened but in general the disease is focused on the LV. In typical cases of HCM the LV systolic function (ejection fraction) is hyperdynamic and *diastolic dysfunction* is considered the major abnormality. However, *systolic dysfunction* can develop and is often observed in HCM cats presented in chronic CHF. Dynamic LV outflow tract obstruction (LVOTO) is commonly observed (HOCM); its overall clinical importance is unresolved in comparison to humans where it is a risk factor for clinical signs and sudden death. LA dilation occurs with progressive LV dysfunction, predisposing to arterial thromboembolism.
The natural history of feline HCM[4,5] can be benign or lethal (CHF or ATE); relatively brief or protracted; and some cats remain asymptomatic for many years before succumbing (if ever) to the disease. Even severely affected cats might be asymptomatic when first diagnosed. When present, severe left ventricular outflow tract (**LVOT**) obstruction or ventricular tachycardias have been (possibly) associated with syncope and sudden cardiac death. The overall frequencies of disease in the general population is high (15%?), the rate of complications largely unknown (and based in part on echocardiographic criteria used to define HCM). Importantly most cats with HCM remain asymptomatic.

Clinical Epidemiology

Feline HCM is characterized by thickening of the left ventricular walls and papillary muscles unexplained by congenital disease, hypertension, or endocrinopathy. It is considered an adult onset, genetic (or idiopathic) disease in most cats and can occur in both younger cats (<1 year of age) and older individuals. Because of the variable age in onset across feline breeds, and morphologic changes that can occur over time, it is a challenging disorder to pinpoint in terms of onset of disease. Male cats seem predisposed to HCM in most studies (estimated 3:1 M:Fe). (Additionally intact males are bigger and more likely to have somewhat thicker ventricles even normally). There is no reported evidence of a sex-linked mode of inheritance. Some specific breeds at risk for HCM include the Maine coon, Persian, Ragdoll, Bengal, Sphinx (Sphynx), American and British short-hair cats, and Norwegian Forest cat.

Considering the prominence of HCM in the feline population and prevalence in certain breeds, it is not surprising that *genetic mutations* have been identified in some affected cats (including mutations of myosin binding proteins in Maine coon cats (A31P) and in Ragdoll cats (R820W); recently a genetic test for HCM has been reported in the Sphynx breed (ALMS1 mutation).

Limited genetic testing is available currently (NCSU University). These tests are mainly used by breeders, but veterinarians should be aware of these when counseling those clients. At times there might be value in performing these genetic tests in ambiguous clinic cases involving breeds where genetic mutations have been reported. When counseling breeders the conventional wisdom has been homozygous 'positive' cats for the mutation should not be bred; whereas heterozygous cats might be considered suitable for one breeding if mated to homozygous 'negative' and ideally unrelated cats. Importantly, the majority of cases of HCM are encountered in mixed-breed cats, and genetic testing is unavailable for these cats.

Pathology & Cardiac Dysfunction – Correlations to Clinical Findings

Pathology The *variable pattern of ventricular hypertrophy* in this disease, ranging from concentric to focal (segmental) thickening, can be demonstrated at autopsy or by 2D echocardiography. Generally the heart weighs >20 grams in affected cats. The pattern of segmental or regional hypertrophy can influence the prognosis. For example, asymmetric free wall hypertrophy is often associated with significant LV dysfunction and progressive left atrial (LA) dilation. Conversely, focal subaortic, focal mid-septal, or isolated papillary muscle hypertrophy are often well-tolerated forms of HCM. However, these lesions progress in some cats and thus warrant follow-up. As noted above, a specific variant of LV hypertrophy in older cats is a subaortic septal thickening associated with a dilated aorta. Whether this is actually a genetic HCM, or a degenerative aortic dilation (aortoannular ectasia) in which altered flow stimulates focal hypertrophy is undetermined. In most cases, this form is benign.

The classic histologic findings of HCM are hypertrophy of cardiomyocytes with fiber disarray and interstitial fibrosis, although these may be challenging to identify (or absent). Intramural coronary arteries are narrowed with foci of myocardial infarctions or interstitial replacement fibrosis observed. Some cats with HCM progress to a form of RCM or nonspecific cardiomyopathy in what has been termed "end-stage" or "burned out HCM." In each of these conditions, *extensive myocardial fibrosis* is evident histologically.

The *right ventricle* is less often involved with HCM but can be affected in both structure (thickening) and function (occasionally impaired). The frequent finding of pleural effusions and jugular distension and right atrial dilation in cats with end-stage HCM also suggests some role for RV involvement or secondary dysfunction due to elevated left atrial pressure or stiffness (pulmonary hypertension is not considered common). Septal thickening of HCM seems to facilitate dynamic RVOT obstruction, which is another common reason for a cardiac murmur in cats with HCM.

Ventricular Function in HCM Left ventricular *systolic function* in most cats with HCM is hyperdynamic, but there can be regional or focal reductions that might require advanced (tissue) echo studies to identify, and systolic function can slowly degrade over time. When HCM evolves to an end-stage form, the LV free wall, septum, apex or the entire left ventricle can become hypokinetic. Infarctions or myocardia replacement fibrosis, with marked wall thinning,

might be observed.[5] Should atrial fibrillation develop, active atrial function is lost, ventricular function further impaired and this can precipitate severe CHF or an ATE event. Dynamic and labile pressure gradients between the LV and aorta are found frequently and confer the title of "obstructive" to HCM. These gradients stem from systolic anterior motion (**SAM**) of the mitral valve causing hypertrophic obstructive cardiomyopathy (**HOCM**). Invariably SAM causes some degree of mitral regurgitation (**MR**) which is seen as an eccentric jet away from the anterior leaflet on color Doppler imaging. Other jets of MR might be observed during Doppler imaging; often these are silent to auscultation. Although SAM has not been clearly associated clearly with a worsen prognosis (the presence of a murmur allows many asymptomatic cats to be identified), increased myocardial injury as evidenced by elevated cardiac troponin-I (cTnI) has been reported in cats with dynamic left ventricular outflow tract obstruction (**DLVOTO**), and this might represent a reason to treat in severe cases. The mitral valve can elongate in this disease; the major differential diagnosis in young cats is primary mitral valve malformation. Midventricular obstructions are also common between the thickened septum and papillary muscles; the significance of these is unknown.

The presumptive cause of CHF in feline HCM is *LV diastolic dysfunction*, which means that elevated left atrial and pulmonary venous pressures are required to fill the LV. These abnormalities can be documented using advanced Doppler studies. Diastolic dysfunction evolves gradually, often taking years to progress. Initially, mild (Grade I) dysfunction is observed due to impaired relaxation that shifts LV ventricular filling to late-diastole via vigorous LA contraction. In some cases, severe diastolic heart failure (Grades III and IV) eventually develops from increased LV chamber stiffness. It is likely that myocardial fibrosis is instrumental in this progression. However, to this date, treatments that prevent cardiomyocyte death and collagen replacement have been demonstrated in cats. The noncompliant LV restricts ventricular filling and demands chronically-high venous pressures for cardiac filling.

Decompensated CHF is often related to stressful events (presumably with prolonged sinus tachycardia that abbreviates diastole and coronary perfusion). Abrupt impairment of myocardial perfusion or high myocardial oxygen demand seemingly causes rapid-onset or "flash" pulmonary edema in some cats, necessitating emergent treatment. Sometimes diastolic function seems to improve with elimination of the stressor, allowing a reduction in diuretic therapy over time. Some of these cats also reduce their wall thickness, suggesting a state of *"transient myocardial thickening*," likely secondary to myocarditis.

Progressive atrial dilatation and dysfunction go hand and hand with progressive loss of ventricular diastolic (and systolic) function. Thus, *atrial volume or size* as observed by echocardiography - or less objectively by radiography - stands as *one of the best indicators of disease severity and short-term prognosis*. Left atrial *function* can be measured by 2D or Doppler methods and can provide further prognostic information. Cats with moderate to severe LA dilation or dysfunction need antiplatelet/antithrombotic therap(ies) as well as careful home monitoring of respiratory rate and activity to detect any progression to CHF.

Clinical Examination in Feline HCM

The prevalence of HCM is debated related to the diagnostic criterion used for feline wall thickening. The disease is common and among the most frequent reasons for a heart murmur in cats. Most cats with HCM are asymptomatic and recognized when a heart murmur or gallop sound is discovered during a routine exam, although it is emphasized that heart murmurs are variable in the HCM population and common in the normal/healthy cat population. Occasionally cardiomegaly is recognized as an incidental finding in a cat radiographed for another reason.

History There are no unique clinical findings of HCM, and symptomatic cats can present with any combination of signs. Identification of a murmur, gallop sound, arrhythmia, or cardiomegaly often prompts referral for echocardiography. Increasingly, abnormal biomarker results (especially NT-proBNP test) prompt further cardiac evaluation. The clinician must be mindful that secondary cardiomyopathies develop from other diseases such as systemic hypertension, and that other organ systems can be affected. Thus, a thorough physical examination and an open mind are critical to accurate and efficient diagnosis.

Reduced activity and respiratory difficulty (tachypnea, hyperpnea, and respiratory distress) are typical findings if pulmonary edema or pleural effusion from congestive heart failure (CHF) supervene. Some cats with heart disease cough, but this is far less common (compared to dogs). Chronic coughing in a cat with cardiomegaly is more likely to represent bronchopulmonary (or heartworm) disease with cor pulmonale rather than left-sided CHF, although there are exceptions (especially with congenital heart disease). Urgent presentation to the veterinary hospital is likely following a bout of ATE owing to the acute onset of pain, paresis and vocalization in witnessed cases (discussed later).

Stress, fever, moderate-to-severe anemia, thyrotoxicosis, anesthesia, surgical procedures, trauma, or fluid therapy can precipitate CHF or ATE in a previously stable cat with cardiomyopathy. Prior therapy with long-acting corticosteroids (especially Depo-Medrol®) is considered another risk factor for development of CHF; however, the precise mechanisms underlying this association are unresolved. It is perhaps a form of transient myocardial thickening.

Physical Examination Findings in feline cardiomyopathies vary widely. Many cats with HCM are healthy. Cardiac, vascular, and respiratory problems are most often identified in cats with symptomatic disease; however, clinical findings referable to other organ systems might be evident. Often heart disease is discovered serendipitously following cardiac auscultation or thoracic radiography while evaluating a cat for another disorder.

Cardiac auscultation of cats with cardiomyopathy often reveals an extra diastolic sound or gallop. As noted above under "pathophysiology," *gallops* are classically considered indicators of impaired or altered ventricular filling. Without phonocardiography it is difficult – if not impossible – for most clinicians to separate the various gallop sounds – or the systolic clicks –

that can create a “triple-sound” or galloping cadence in a cat. However, these transient sounds carry somewhat different clinical consequences, although there is overlap. For example, an isolated atrial (S4) gallop is generally a sign of mild to moderate diastolic dysfunction, representing a transient increase in atrial pressure compensating for impaired ventricular relaxation. In fact, this can be a misleading finding in older hospitalized cats where atrial gallops unassociated with cardiomyopathy can sometimes be heard. This is likely from a normal but aging ventricle that develops mild diastolic dysfunction (similar to humans and dogs). In contrast a persistent ventricular (S3) or summation (S3 + S4) gallop is more ominous, especially in a cat with tachypnea, and often signals advanced diastolic dysfunction, a noncompliant ventricle, and elevated venous pressures predisposing to CHF. *Systolic clicks* also occur in cats and can be confused with (diastolic) gallops. These might indicate mitral valve malformations, HCM, or some other condition. Sometimes gentle progressive pressure on the nasal planum for about 5 seconds will induce a transient slowing of the heart in about 10-20 seconds, and this vagal maneuver might help an astute examiner better determine the timing of the extra sound.

Cardiac murmurs are common in cats. Pathologic and functional (physiologic) murmurs can sound similar, making the genesis of heart murmurs difficult to sort out. Heightened sympathetic tone, peripheral vasodilation, and altered blood viscosity, are important mechanisms for physiological heart murmurs and variably occur with thyrotoxicosis, anemia, fever, volume depletion, following sedatives (ketamine), and most often during the fright of a veterinary hospital visit. One interesting source of functional murmurs observed by color Doppler echocardiography is hyperdynamic contraction of the right ventricle leading to dynamic obstruction in the proximal right ventricular outflow tract. Although some believe this is only an artifact from excessive stethoscope or probe pressure, the author believes it is relatively common in both healthy and cardiomyopathic cats and need not be iatrogenic.

In general, louder murmurs tend to indicate primary heart disease but this guideline is not absolute. Increased heart rate relates to sympathetic activation, and hyperdynamic ventricular contraction. This can create turbulence in the structurally normal left or right ventricle, and also accentuate pathologic flow in a hypertrophied chamber. Murmurs of MR and LVOTO due to SAM of the mitral valve increase with higher sympathetic tone. Thus, murmurs that increase in intensity during faster heart rates can be functional (nonpathologic) or organic (pathologic).

When caused by cardiac disease, murmurs are usually related to some form of cardiomyopathy (or to a heart malformation), as opposed to some degenerative valve disease. Systolic murmurs in HCM can be secondary to SAM, MR, or dynamic obstruction in the mid-ventricle from hypertrophied muscle. Other potential sources for a systolic murmur is ejection of blood across a dorsal septal bulge and into a dilated aorta due to HCM or to DUST.

Examination pointers: Feline auscultation is hard! Even when a consistent examination approach is undertaken, a pediatric chest piece is used, and the cat is examined in sternal

recumbency. The heart rate creates substantial challenges for timing of auscultatory events. Key findings to detect are: abnormal rate or rhythm, pauses (often from PVCs), extra sounds, and murmurs. Nearly all feline murmurs are *systolic*. Diastolic murmurs are rare, generally due to severe aortic root dilation and aortic regurgitation or infective endocarditis. Continuous (or "long-systolic") murmurs are identified cranially in cats with patent ductus arteriosus.

In the author's experience, it is not helpful to designate valve areas for auscultation in cats; instead, most systolic murmurs are characterized by their location relative to the sternum and palpable cardiac impulse. As a gross generality, murmurs loudest at the apex (caudal heart border) are more likely to be caused by mitral regurgitation (MR) from cardiomyopathy or a valve malformation or by midventricular obstruction. In contrast, murmurs more intense at the cranial right sternal edge are suggestive of a ventricular septal defect, functional ejection murmur, or turbulent flow into the ascending aorta. Murmurs stemming from SAM of the mitral valve tend to be loud at both locations. These observations are guidelines at best and have not been tested critically in blinded auscultation-echocardiographic studies. When murmurs are loud, the vibrations can transmit widely, adding ambiguity to the diagnosis.

Auscultation of the heart should be coupled with *examination of the respiratory system*. Tachypnea or respiratory distress in a cat should prompt keen observation of the pattern of ventilation. Significant findings include the presence of loud airway noises (suggesting large airway obstruction), wheezes or rhonchi (suggesting bronchial disease), crackles (suggesting edema or parenchymal disease although this finding is variable), or a pleural fluid line. Distressed cats often require oxygen and sedation along with urgent therapy for upper airway obstruction (intubation), asthma (inhaled or injected bronchodilators), pulmonary edema (diuretics), or pleural effusion (thoracocentesis) before proceeding to radiography or other evaluations.

Pulse abnormalities Abnormal arterial and venous pulses might point to a CV disorder. The jugular venous pulse might be prominent, or the veins grossly distended, in cats with CHF, cardiac tamponade, cor pulmonale, or circulatory volume overload. The latter situation is commonly observed when a cat with anemia, renal failure, or thyrotoxicosis is administered substantial volumes of sodium-replete fluids. Hyperdynamic arterial pulses are typical of bradycardia (heart block), hyperthyroidism, and anemia. Irregular pulses should be considered abnormal in cats and prompt an ECG to identify premature complexes or periods of atrioventricular block.

Loss of a peripheral arterial pulse in a cat is supportive of *arterial thromboembolism* (ATE). Vascular signs of ATE typically stem from an underlying cardiomyopathy (or myocarditis), although thrombi also can develop with pulmonary malignancies. A thromboembolism usually originates in the left auricle and travels to the terminal aorta. Smaller thrombi can cause myocardial infarction, thrombotic stroke, forelimb monoparesis, renal infarcts, or rarely mesenteric ischemia with severe colic. Diffuse intra-abdominal ischemia also can be caused by a massive aortic thrombosis. Signs related to embolism to a forelimb can be relatively brief

(hours). Terminal aortic embolism is generally more severe, and signs might persist for hours to weeks, though many cats recover limb function if given sufficient time and care (see later). The physical diagnosis of terminal aortic embolism is straightforward and characterized by vascular, musculoskeletal, and neurological deficits, and associated laboratory abnormalities (elevated CK, AST, muscle-derived ALT). Limb edema is not an early sign of ATE, though it might be observed days or weeks after the event as a consequence of severe muscle injury (rhabdomyolysis). This can predict a poorer chance for full recovery of function.

Other Physical Examination Findings – Additional clinical signs are possible in cats with cardiomyopathy. Examination of the ocular fundus should be undertaken in cats with cardiac signs, to screen for hypertensive retinopathy in particular and for retinal degeneration when a diagnosis of DCM has been made. The general examination should consider the cervical region (for thyroid masses); the kidneys (as a risk factor for hypertension or as targets for hypertensive injury or thromboembolic events); and the mucous membranes (for signs of anemia, hypoperfusion, or cyanosis). Hypothermia is often observed in cats with ATE; when profound, is a poor prognostic factor.

The triad of reduced body temperature, heart rate, and blood pressure is highly suggestive of *cardiogenic shock*, a condition that demands aggressive inotropic therapy (see below). This is usually distinguished from septic or hypovolemic shock by the presence of cardiomegaly and fluid collections attributable to CHF. Occasionally cats demonstrate evidence of both cardiogenic and non-cardiogenic shock. This may relate to dehydration if clinical signs have been present for some time or relate to a concurrent disorder. There is some speculation that impaired perfusion of the gut and pancreas might add a vasculogenic component to shock and some cats with heart failure; these cats will not respond to inotropic support alone.

Weight loss is compatible with systemic disease of any origin but is especially common in hyperthyroidism and chronic kidney disease and in some cats with chronic CHF. Abdominal distension related to hepatomegaly and ascites can develop in cats with cardiomyopathy but are relatively uncommon except in cats with atrial standstill, primary right-sided heart disease (right ventricular cardiomyopathy), or atrial fibrillation.

Diagnostic & Laboratory Studies in Feline Cardiomyopathies

A cat *symptomatic* for CHF or an ATE does not pose a diagnostic challenge; there are clear pathways to obtain a definitive diagnosis. The situation is far different in the *healthy cat* with a cardiac murmur. A number of *screening tests* might be useful in assessing the cause of a heart murmur. These include thoracic radiography, 6-lead electrocardiography, and circulating biomarkers, namely NT-proBNP and the standard and high-sensitivity cardiac troponin tests.

Neither standard ECG nor routine thoracic radiographs are cost-ineffective when applied to healthy cats or cats with mild HCM, normal LA size, normal heart rhythm, and no respiratory signs. Certainly if each the above screening examinations are applied in a cat with a murmur caused by cardiomyopathy, the likelihood of identifying structural heart disease is relatively

high. However, the attendant veterinary costs are similarly great and perhaps 50% of cats with systolic murmurs will have normal or equivocal examinations. For this reason, many veterinarians simply advocate obtaining an echocardiogram when assessing asymptomatic cats with a heart murmur. When this option is not viable for client or other reasons, the NT-proBNP test, particularly the analytical laboratory test, is useful (see below).

Blood Pressure – Systemic arterial BP is usually normal in cats with cardiomyopathy unless the cause of myocardial disease is systemic hypertension. The cat with profound CHF or ATE might be hypotensive, with hypothermia and reduced peripheral perfusion. Cardiogenic shock is not specific for any particular form of cardiomyopathy, but often suggests an acute event such as an infarction or thromboembolism. Technical details of BP recording are critical.

Diagnostic Imaging – Echocardiography and thoracic radiography each play key roles in the assessment of cats with HCM. Point of care ultrasound can be very useful for identifying pleural effusions, intrapulmonary water (B-lines), and potentially left atrial dilation which argues strongly for a diagnosis of CHF in symptomatic cats.

Radiography – The most common *radiographic features* include elongation of the silhouette (LV hypertrophy) and bulging of the left auricle on the VD projection – the latter is only seen in moderate to severe LA dilation. Pulmonary infiltrates in CHF are often bilateral and somewhat more ventrally dependent in the perihilar region (between heart and diaphragm) than for dogs. Pulmonary vascular markings (both arteries and veins) are often increased in cats with CHF. Pleural effusions are typically small in cats with acute pulmonary edema, but volumes can be moderate to large in cats with chronic congestive failure or end-stage myocardial disease of any type. Quantitatively CHF is the most common reason for pleural effusions in cats and therefore cardiac disease should always be suspected. Pleural effusion in cardiomyopathy is primarily related to left-sided heart disease but there is undoubtably fluid retention that might pertain to impaired cardiac output in general. Many cats with pleural effusions have prominent right atrial chambers (biatrial dilation) and clinical examination prior to diuretics often demonstrates jugular venous distention suggesting at least clinical, biventricular heart failure.

Echocardiography – Cardiac ultrasound is necessary for definitive diagnosis as radiography and ancillary studies such as ECG and biomarkers do not sufficiently distinguish HCM from other forms of cardiomyopathy. High resolution imaging (transducers of 7MHz or higher) are usually needed, especially in cases that are mild to moderate in severity with normal LA size. LV hypertrophy unexplained by other diseases (that can include papillary muscle thickening) is the requirement for diagnosis. The precise cut-offs for identifying increased wall thickness are debated, and this lack of agreement exerts a profound effect on many clinical studies of feline cardiomyopathies inasmuch as cats are variously classified as “normal” or “affected” based on different hypertrophy cutoffs. Probably most cardiologists would agree that LV wall thicknesses less than about 5.2 mm (at end-diastole, measuring one endocardial thickness) argue against HCM; diastolic thicknesses of $\geq$6 mm strongly support a diagnosis of LV hypertrophy; and the

range between 5.5 to 6 mm is considered equivocal (or at least debated in terms of normality). Additionally, LV wall thickness relates to body weight (allometric scaling), with mean values increasing ≈1 mm across the typical small to large cat weights – a tiny yet clinically relevant value. When echocardiography with Doppler shows systolic anterior motion (SAM) of the mitral valve, with eccentric jet of MR and dynamic LVOTO, the diagnosis is more secure. Severe LVOTO (e.g. velocities exceeding 4 m/s) is sometimes found and could represent an indication for beta-adrenergic blockade (see Pathophysiology). Intraventricular or mid-cavitary obstructions often develop between the ventricular septum and papillary muscles when there is LVH *from any cause* (or volume depletion); this can also be identified by Doppler studies.

Electrocardiography – An *abnormal ECG* is relatively specific but generally considered insensitive for the diagnosis of HCM. Potential abnormalities include P-waves or QRS complexes of increased amplitude or duration; prolonged QT interval; left axis deviation (with increased voltages); and cardiac arrhythmias. No specific ECG finding can discriminate the various forms of cardiomyopathy in cats. In one study a prolonged QT interval was evident in cats with HCM. A left axis deviation (with increased voltages) is suggestive of LV hypertrophy, so long as the voltages are also increased. As noted previously, persistent cardiac arrhythmias have been generally associated with structural heart disease of some sort in cats.

In terms of specific feline criteria, widened (≥0.4 sec) or tall (≥0.25 mV) P-waves predict the finding of atrial enlargement on echocardiography. In the author's experience, R-waves or S-waves exceeding 0.7 in any frontal plane lead, or a left axis deviation with voltages of >0.7 mV in leads I or aVL are suggestive of LV disease. When the any ventricular waveform is ≥ 1 mV, cardiomegaly is diagnosed. Right axis deviation or hypertrophy patterns (S-waves in leads I, II, III) and intraventricular conduction disturbances are more common with restrictive, right ventricular, and nonspecific cardiomyopathies. Congenital heart defects are also a cause of high voltage or altered electrical axis in cats.

Identification of a suspected heart rhythm disturbance is the principal indication for an ECG in a cat with suspected cardiomyopathy. Since sinus arrhythmia is uncommon in the cat undergoing veterinary examination, an irregular rhythm as well as a persistent rate <150 or >240/min should prompt an ECG examination. Persistent or recurrent arrhythmias are relatively uncommon in cats, but seem more common with RCM, myocarditis, and ARVC compared to HCM. Holter ECG studies have shown that cats with HCM do have more ventricular ectopy than controls, however, this does not mean antiarrhythmia therapy is indicated. Infrequently, an arrhythmia predates the eventual appearance of a structural cardiomyopathy. Transient atrial standstill of uncertain mechanism is sometimes observed in cats with cardiogenic shock; it usually abates if the cardiac output and body temperature increase.

Routine Clinical Laboratory Tests – A serum biochemistry profile might demonstrate abnormalities related to heart failure, ATE, or an underlying systemic disease. Biomarkers, in particular NT-proBNP and cardiac troponin-I (cTnI), are released from diseased ventricles, and

these are the most commonly used "biomarkers" in feline cardiomyopathy as discussed below.

Renal function is often impaired in cats treated for CHF with diuretics and angiotensin converting enzyme (ACE) inhibitors. The serum creatinine and urea nitrogen should be followed whenever dosages are adjusted. Mild to moderate azotemia (BUN <60 mg/dl) is common with acute CHF therapy and might persist in cats receiving high dosages of diuretics or ACE-inhibitors, or those affected by intrinsic kidney disease. As a differential, remember cats with LV hypertrophy due to hypertensive heart disease often have chronic kidney disease with azotemia and hypokalemia, along with an abnormal urinalysis. Severe azotemia can occur in the setting of suprarenal ATE.

Other clinical laboratory tests are relevant to the cat with cardiomyopathy. The serum creatine kinase, AST, and ALT (of apparent skeletal muscle origin) are elevated dramatically in ATE. The AST will be significantly higher than ALT when caused by striated muscle injury. These enzymes elevations can help identify ATE in a cat with severe but rapidly improving paresis of a forelimb. Serum thyroxine should be measured in older cats (> 7 years of age) showing any cardiac signs to exclude hyperthyroidism as a potential cause. A complete blood count might demonstrate anemia or evidence of inflammation, conditions that might allow for a functional heart murmur. Heartworm antibody and antigen tests are relevant when a cat lives in, has traveled to, or has relocated from a heartworm-endemic area. Lastly, in cats with DCM, a whole-blood taurine concentration might indicate if the etiology is a dietary deficiency in this amino acid.

A cytologic and biochemical evaluation can be instructive in the differential diagnosis of pleural effusion. Analysis generally reveals a modified transudate in CHF, often with a predominant population of small lymphocytes and mesothelial cells. Chylothorax is another common finding in severe, chronic CHF of cats, and can be confirmed by measuring serum versus fluid triglyceride concentrations (the latter is higher). Cats with chylothorax can develop a prominent neutrophilic reaction mixed into a mononuclear cell population, which can be confused with pleuritis. Pleural fibrosis (chylofibrosis) can develop making thoracocentesis more dangerous.

Cardiac troponin elevation in the blood (cTnI) occurs when there is myocardial injury or necrosis. It is most valuable when applied to evaluation of the cat with one of the following conditions: 1) arrhythmia of unexplained cause; 2) DCM; 3) cardiogenic shock; 4) CHF that is acute in onset; or 5) when myocardial infarction is suspected. Markedly elevated cTnI in these settings might suggest myocarditis or ischemic heart injury. Echocardiographic evidence of a regional or diffuse wall motion abnormality is also supportive of vascular-induced muscle injury. Sometimes these conditions improve dramatically following a period of medical stabilization, so a severe elevation in serum troponin (e.g. >10 ng/ml) might influence prognosis and treatment decisions in these cases. The standard cTnI also might be elevated in asymptomatic HCM; however, too often the results return as equivocal. In one study differences in cTnI values among healthy cats and those with asymptomatic HCM (cutoff: 0.163 ng/ml) was insensitive but specific for separating normal from HCM. Additionally, (Siemens's) high-sensitivity cTnI values >0.06 ng/ml showed good diagnostic performance in one study.

Natriuretic peptides (reference laboratory NT-proBNP and Cardiopet® SNAP® test) carry good clinical utility for identifying previously undiscovered heart disease, although *the patient population sampled will influence the predictive value of these tests*. Aside from echocardiography, the feline NT-proBNP test appears to provide the best balance between specificity and sensitivity in the recognition of cardiomyopathies, although this has been questioned in a recent study from Taiwan when applied to cats from general practice. Overall an emerging literature suggests that the NT-proBNP can provide a cost-effective screening tool for excluding important structural heart disease in many cats *with heart murmurs*. This test can better separate "normal" from abnormal heart murmurs, especially if "cut-offs" are clearly defined and testing is not done indiscriminately (e.g. only applied to cats with murmurs, gallops, or signs of respiratory dysfunction/possible CHF). This biomarker might also help predict future CHF in cats with LA dilation when values are very high (>700 pmol/L).

The reference laboratory test usually points to values ≥100 pmol/L as abnormal although this is a somewhat arbitrary value, and some studies show lower values (closer to 59) as the optimum cutoff. The currently available in-house SNAP test from IDEXX is a useful tool when results are needed rapidly. Although designed for blood it can also be run on *pleural effusion* fluid. This test becomes positive "around" 150 pmol/L. When "negative" it indicates a low risk of significant (i.e. moderate to severe) myocardial disease (high negative predictive value). In cats with murmurs who are not imaged further, this test can be repeated in 6 months for more assurance in a healthy cat with a murmur. A positive SNAP (color change same as the positive reference spot) carries some potential for a false positive, but overall the sensitivity/specificity of the test is about 85%, at least in referral populations. When the patient rest result is darker than the reference positive "spot" the likelihood of significant disease is quite high and usually means values exceeding 200 to 270 pmol/L. A positive SNAP test is somewhat less useful for a symptomatic cat because the "cut-off" for dyspnea due to cardiomyopathy versus noncardiac respiratory distress is different. A higher cut-off value, greater than ~270 pmol/L in one study, successfully distinguished cats with respiratory signs caused by CHF from those related to primary respiratory disease. (As methodologies and reference values have changed over the years, the clinician should use the standards and guidelines reported by the reference laboratory; currently if the patient test result is darker than the positive control the value is likely 270 or higher). As with any laboratory test, there will be exceptions and ambiguous results, so the clinician must exercise appropriate judgment and integrate all clinical data when interpreting the results of NT-proBNP. To summarize: the negative predictive value of a "low" test value is very good for both healthy and symptomatic cats. The positive predictive value of a strong positive (darker than the positive control spot) suggests a value >270 pmol/L and likelihood of cardiomyopathy or other heart disease. While most normal cats with murmurs have values <100 pmol/L, there are grey zones between 100 and 150 (and even up to 200) pmol/L, and clients should be so-advised (in part because the test is less effective for diagnosing "mild" HCM). Importantly, one should NEVER treat a cat based only on a biomarker test!

Risk Stratification in Feline Cardiomyopathies

As in humans, there are seemingly different stages of HCM that range from "occult" disease with genetic mutations and subtle myocardial changes near or below thresholds of clinical detection (meeting criteria for ACVIM consensus **Stage A**); established hypertrophic cardiomyopathy that is easy to diagnose by Echo but well-tolerated with no overt clinical signs (**Stage B1 or Stage B2** for cats with moderate to severe left atrial (LA) dilation), and cats that develop the overt clinical manifestations of congestive heart failure (CHF) or ATE (ACVIM **Stage C**) or progressive end-stage CHF (ACVIM **Stage D**). The morphology of HCM can change over time progressing to "end-stage" or "burned out" HCM. These cats demonstrate progressive LA dilatation, impaired LV systolic function (often segmentally), and higher risks for CHF and ATE.

The REVEAL study[4] has provided detailed prognostic information about the long-term effects of feline HCM. This study involves over one thousand cats from around the world and reported the risks for CHF, ATE, and cardiac death in this multicenter study. They authors showed that "*…during the study period, CHF, ATE, or both occurred in 30.5% and cardiovascular death in 27.9% of 1008 HCM/HOCM cats. Risk assessed at 1, 5, and 10 years after study entry was 7.0%/3.5%, 19.9%/9.7%, and 23.9%/11.3% for CHF/ATE, and 6.7%, 22.8%, and 28.3% for cardiovascular death, respectively.*" These data validate the long term; negative influence of HCM on affected cats overall and provides some useful information for practicing veterinarians and cardiologists alike when counseling owners about follow up and outcomes.

Increased left atrial size and reduced LA function (including left auricular function and presence of spontaneous echo contrast/ "smoke" or thrombus) are major risk factors predicting ATE or CHF in cats with cardiomyopathies. Extreme concentric or LV freewall hypertrophy (9 mm or more in diastole) are others. Additional factors that might affect prognosis and therapeutic decisions include the echocardiographic findings of systolic dysfunction of the LV, regional LV wall motion abnormalities (suggesting prior infarction or myocyte fibrosis), severe diastolic dysfunction of the LV (poor compliance/high filling pressures measured by Doppler echocardiography), and unambiguous myocardial scarring or mural thrombus. Atrial fibrillation or complicated ventricular ectopy in HCM represent other concerns for poor outcomes.

When clinical signs do develop, these are explained mainly by left-sided CHF, complications of ATE, LVOTO, or arrhythmias. Up to this point, most treatments have evolved empirically and (at the time of this writing) there are no pivotal, prospective studies available for delaying or treating CHF in feline cardiomyopathies. Retrospective studies have suggested a role for various treatments, but none of these report fulfill criteria for a high-grade clinical trial (prospective, randomized, multicenter, double blinded, sufficiently powered with suitable controls, well-defined subjects, and sufficient events). Of course, a cat with cardiomyopathy secondary to systemic hypertension or hyperthyroidism will be treated and probably benefit most from control of the underlying disorder (such as amlodipine plus benazepril or telmisartan for moderate/severe systemic hypertension). The authors approaches are offered below.

Asymptomatic Hypertrophic Cardiomyopathy

The treatment of asymptomatic HCM is controversial with no clear benefit of any drug shown for asymptomatic cats with mild disease. Clients should be advised of this information prior to writing prescriptions for a difficult-to-treat species. A single-center prospective study failed to demonstrate any 5-year survival benefit of *atenolol*, although the study samples were small with low event rate. In a colony of cats with HCM, neither *ramipril* nor *spironolactone* significantly altered hypertrophy, diastolic function, or MRI-estimated fibrosis in a small study in a Maine coon cat colony. These were healthy HCM cats and the effect of these drugs in advanced disease or in cats with CHF might be different. *Mavacamten* (inhibitor of contractility that inhibits myosin ATPase and reduces the number of actin-myosin cross-bridges) is under clinical investigation; this recently (USA-human) approved drug reduces LV contractility and outflow tract obstruction. Preliminary data in cats suggest a statistically-significant, but clinically small, small reduction in LV hypertrophy.

Dynamic LVOTO is a risk factor for syncope and sudden death in people with HCM, but some reports suggest the opposite situation for cats (an observation confounded by the frequency of cardiac murmurs found in obstructive HCM, when compared to cats with non-obstructive forms of disease that are under-diagnosed until symptomatic). Despite the lack of evidence, many cardiologists treat dynamic LV obstruction associated with HOCM. There is one report that indicates substantially higher cTnI concentration in cats with HOCM, which might mean the increased LV systolic pressure causes ischemia or additional cardiomyocyte injury. Severity of obstruction probably relates to the degree of sympathetic tone at the time of the examination. Maximal LVOT velocities of ~4m/s to 5 m/s (indicating gradient of ~65 to 100 mm Hg) might be worth treating, assuming the owner can easily medicate the cat.

Atenolol is usually selected for LVOTO because it is well-tolerated and better reduces heart rate, dynamic obstruction, and intensity of murmurs compared to diltiazem. Beta-blockade also confers *theoretical* advantages of diminishing demand ischemia, prolonging ventricular and coronary filling periods, and protecting against sympathetically induced arrhythmias. However, none of these benefits have been proven or translated to major clinical endpoints, such as 5-year survival. Atenolol doses (6.25–12.5 mg/cat PO bid) are usually adjusted based on exam room heart rate with a target of 120-160/minute while in the carrier. In asymptomatic HCM cats with moderate LA dilation (two-dimensional, long-axis LA diameter exceeding 19 mm or LA/Ao short-axis exceeding 1.7 to 1.8), the atenolol dose might be reduced or discontinued (as it can depress LA function). In those cats, antiplatelet therapy is prescribed (clopidogrel - see below) and the client is dispensed a “rescue” prescription of furosemide and optionally tramadol should the cat develop resting tachypnea or signs of an ATE supervene. Clients are duly instructed to seek prompt care for dyspneic or paretic/suddenly painful cats.

Congestive Heart Failure

Management **in hospital** for the cat with acute or severe CHF begins with gentle handling. Cats

with pulmonary edema are managed by considering treatments using the "SO-FINE" approach: **S**edation (*butorphanol* 0.2–0.3 mg/kg IM), ***O**xygen* (40–50%), ***F**urosemide* (2–3 mg/kg, IV/IM), ± an ***I**notrope* (see below), ±***N**itroglycerine* (1/8 to 1/4 inch of 2% NTG ointment) for severe pulmonary edema. The "E" is for "**E**xtra" therapy such as *thoracocentesis* as needed. Once diuresis occurs (keep checking for urine!) and dyspnea improves, the furosemide dose is reduced (1–2 mg/kg q12h). Most of these treatments are insufficiently evaluated in clinical studies. The use of inotropic drugs such as pimobendan is controversial for the treatment of cats with CHF when failure is due to HCM, especially if there is dynamic obstruction (HOCM). However, for the cat with impaired systolic function pimobendan is recommended (1.25 mg PO bid is given to the average sized cat). The author also uses pimobendan initially for all cats with moderate to large pleural effusions, but not for cardiogenic edema, especially when there is a systolic murmur that suggests LVOTO, and the edema responds well to diuretics.

For cats with cardiogenic shock (hypothermia, bradycardia, systolic BP<70 mm Hg) the inotrope *dobutamine* can be lifesaving (regardless of the type of cardiomyopathy). Dosing starts at 2.5 micrograms/kg/minute and is up-titrated to 5-10 micrograms/kg/min with therapeutic targets of rectal temperature of >100 °F (37.8 °C); heart rate >180/minute, and systolic BP >90 mm Hg. As indicated above, when a "FAST" thoracic scan shows systolic dysfunction and no outflow obstruction, pimobendan (1.25 mg/ cat, PO once or twice daily), is also administered.

Thoracocentesis is the most important therapy for moderate-to-large pleural effusions. With the cat sedated, positioned in sternal recumbency, and receiving supplemental oxygen by face mask, a small butterfly catheter or thoracocentesis catheter is inserted in the intercostal space following a local infiltration of lidocaine. When pleural effusions are bilateral, tapping the right thorax might avoid puncturing a dilated left auricle; ultrasound guidance is helpful.

The **home therapy** of chronic CHF centers on administration of furosemide (1–2 mg/kg, PO q.d.–bid). Depending on the clinician's viewpoint, this can be combined with an ACE-inhibitor (enalapril/benazepril: 0.25–0.5 mg/kg, PO q.d and spironolactone (6.25–12.5 mg/cat, once daily) if deemed useful to block the RAAS. Unfortunately, there are no clear data on this although it is known that loop diuretics activate the RAAS and a "pril" + spironolactone should help maintain serum potassium and (potentially) be anti-fibrotic. *Antiplatelet therapy* is initiated (see next section). The aforementioned drugs can be put into a single, tasteless gelatin capsule. Extralabel use of *pimobendan* (~0.25 mg/kg or 1.25 mg/cat PO q12h) provides an additional treatment option for chronic CHF, particularly in cats with end-stage HCM and large pleural effusions or those cats with other nonobstructive forms of myocardial disease. Thus, the author prescribes pimobendan immediately for cats with CHF due to end-stage HCM and for dilated, restrictive, "unclassified," and right ventricular cardiomyopathies, and he holds it in reserve for refractory failure when CHF is caused by HCM, especially HOCM. As noted above, pimobendan should be used with caution in cats with HCM with dynamic LVOT obstruction. Although a retrospective study showed potential (marked) benefit of pimobendan in cats with HCM, a prospective study was less impressive and did not achieve the statistically-significant

endpoint. We simply need more data about this drug in cats. Finally, neither atenolol nor diltiazem is recommended for CHF (both were ineffective in an unpublished multicenter study).

Overall, *potential CHF therapies* follow the memory clue: "*Cats Are For Special People*," representing treatments of ***C****lopidogrel*, ***A****CE-inhibitor*, ***F****urosemide*, ***S****pironolactone*, & ***P****imobendan*. Two caveats are pimobendan is not used for all cases and RAAS inhibition is insufficiently studied. When CHF is refractory to furosemide, *torsemide* (at ~1/10 the furosemide daily dosage) is initiated once or twice daily hoping for a longer duration of effect.

Clients are counseled regarding signs of decompensation (*can't breathe*! / *can't walk*!); how to treat their cat (using pill pockets, *gelatin capsules*, pill guns, etc.); and monitoring activity level, ventilation effort, sleeping respiratory rate (<30 to 35/min is OK), and appetite. Follow-up veterinary examination begins with a medical history and a conversation focused on treatment compliance. A careful physical examination is critical. Diagnostic testing may involve BP, serum biochemistries, thoracic radiography, and cardiac/thoracic ultrasound (fluid checks).

Arterial Thromboembolism & Anti-thrombotic Therapy

Arterial thromboembolism (ATE) is a sudden interruption of blood flow caused by a thrombus that forms proximal to the affected site and is carried by the bloodstream to the location of vascular obstruction. In most cases, the site of origin is the auricle of an enlarged left atrium (LA) from a primary or secondary cardiomyopathy (cardiogenic embolus). Uncommon to rare causes of ATE are infective endocarditis, mitral dysplasia (stenosis) and pulmonary carcinoma. Cardiogenic embolism has been reported in 6-17% of cats with heart disease.

The echocardiographic assessment of the size and function of the LA and its appendage are key when assessing risk of ATE, as covered previously. A previous ATE, presence of LA thrombus, and echogenic contrast ("smoke") pose a substantial risk for a future event. A solid, attached, rounded LA thrombus seen on Echo is a lesser concern than the soft thrombus with a "floating" or "waving" tail protruding from the appendage.

The physical diagnosis of terminal aortic embolism is straightforward and characterized by vascular, musculoskeletal, and neurological deficits, and associated laboratory abnormalities. The muscles become firm to rigid due to ischemia and are associated with elevations of serum creatine kinase, AST, and ALT. Lower motor neuron paresis/paralysis develops. The practices of cutting nails and measuring fore/rear limb glucose/lactate are usually superfluous. Doppler BP crystals can be used to identify presence or absence femoral or distal arterial flow. Thermography is a newer technique to study perfusion and collateral circulation. Radiographs of the thorax should be obtained to document CHF (or lung cancer) if present. In general, heart failure and marked whole body hypothermia are poor prognostic signs. Echocardiography should delineate severity of underlying cardiac disease, which can also influence prognosis.

The first and most important treatment is *analgesia*, ideally with a strong mu agonist for the first 24–48 hours following an event. *Fentanyl* is often used in our practice and provides strong analgesia (beware: thermal dysregulation including hyperthermia). Initiate therapy with 2 to 3

micrograms/kg slow IV bolus and follow that with maintenance infusion of 1 to 3 micrograms per kg/hour. *Methadone* (0.2 to 0.4 mg/kg IV, IM) and *morphine* 0.1 to 0.3 mg/kg IM, slow IV) are other options. In the absence of hypothermia or hypotension, acepromazine (0.025 mg/kg subcutaneously) will sedate the cat further. Pain in most cats is diminished by 36-48 hours allowing transition to buprenorphine (10-20 micrograms/kg IM, SQ, q8-12h, or once daily preparations [Simbadol® 0.24 mg/kg SQ, qd] or long-acting transdermal [Zorbium® - follow label instructions for in-hospital administration]).

Options for acute thrombotic issues include tissue plasminogen activator (tPA), unfractionated or low-molecular weight heparin, and clopidogrel. However, a recent prospective study of tPA failed to show superiority when added to standard (clopidogrel, heparin, analgesia) therapy. If used, dose tPA is dosed at 1 mg/kg (maximal total dosage of 6 mg/cat): 10% of the dose is given as a slow IV bolus and the rest is infused over ~one hour. Therapy with tPA therapy is only offered if the cat presents within 4 to 6 hours of a witnessed event.

Heparin therapy is administered to prevent further thrombosis. Standard (unfractionated) heparin is dosed at approximately 250-300 units/kg IV. Thereafter either a constant rate IV infusion or subcutaneous dosing at approximately 150-250 U/kg subcutaneously q6-8h for 48–72 hours. Preferentially, low-molecular-weight heparin (LMWH) can be administered. These have a smaller molecular weight than unfractionated heparin. *Dalteparin* (100 – 200 IU/kg bodyweight subcutaneously q12h) or *enoxaparin* (1-1.5 mg/kg subcutaneously q12h) are preferred by many criticalists in cats over unfractionated heparin. *Clopidogrel* is administered as well (18.5 mg PO daily; a loading dose of ½ to 1 tablet can be given the first day). Although there are exceptions, most cats destined to show improvement start within 48 to 72 hours of admission. Home care includes, (1) protecting the limbs, (2) daily inspection for subcutaneous or muscle edema, (3) cleaning urine-soaked hair and bedding, (4) providing a soft bed, (5) encouragement to eat, (6) stool softeners (pumpkin or Miramax®), and (6) a low stress area for convalescence. Oral buprenorphine can be prescribed but Zorbium® is probably a better option to prevent drug diversion or inadvertent ingestion. Physical therapy of the limbs is encouraged through gentle passive flexion and extension of the limbs if tolerated. Clopidogrel is continued and low-molecular weight heparin is maintained for two weeks if acceptable to the client.

A variety of approaches have been used for the *prevention of thromboembolism*: (1) aspirin monotherapy (dosed between 5-81 mg/cat q72h), (2) warfarin (~0.5 mg per cat, PO daily), (3) low molecular weight heparins including enoxaparin (1 – 1.5 mg/kg q12-24h) or dalteparin (100 to 200 IU/kg q12-24h), (4) clopidogrel (Plavix, 75 mg tablets, ¼ tablet –18.75 mg – PO once daily); and 5) Factor X_a inhibitors such as apixaban (Eliquis®) and rivaroxaban (Xarelto®). The suggested dosages are apixaban at 0.625-mg/cat PO bid; and rivaroxaban 2.5-mg/cat PO bid or 5.0-mg/cat PO once daily. The FATCAT clinical trial[6] comparing clopidogrel versus aspirin for secondary prevention of ATE in cats that had recovered from ATE indicated superiority of clopidogrel for prevention of recurrent thrombosis (note: no group received both antiplatelet drugs work by different mechanisms, they could be complementary). In this study, median

survival time significantly prolonged with clopidogrel and the median time to either death or the next ATE event was 443 days compared to 128 days in the aspirin group.

Client expectations, cost, and ability to medicate a cat are important considerations when deciding on long-term antithrombotic therapy. The author does not routinely prescribe antithrombotic therapy in asymptomatic cats with a near normal LA, provided auricular emptying velocities >25 cm/s (or LA fractional shortening is >25%). Clopidogrel (¼ of a 75 mg tablet, once daily) is prescribed for the cat with a moderate to severely dilated LA (≥19 to 20 mm in long axis, 2DE or >1.7 to 1.8 LA/Ao by short axis 2DE), or when emptying velocities are reduced (e.g. <20 to 25 cm/s). More intensive prevention should be considered in settings of a prior ATE event, LA thrombus, or spontaneous echo contrast (LA "smoke"). Adding low-molecular weight heparin ($$$), a Factor X_a inhibitor ($$-$$$) or at the least a microdose of aspirin (5 mg/cat/day) to clopidogrel makes clinical sense but efficacy and safety data are lacking. Nevertheless, each of these seem well-tolerated with low risk for bleeding. Plavix and aspirin are bitter and best put into a gelatin capsule (#4 smallest to #2 usually work for cats).

Other Acquired Myocardial Diseases

A number of other cardiomyopathies are encountered in cats. Some of the key features of these are summarized below. The therapy of these has already been considered under HCM.

Restrictive Cardiomyopathy – Feline RCM represents a heterogeneous disorder, and some latitude is used in placing cats within this group as opposed to the "nonspecific" category of feline cardiomyopathy (discussed below). The key pathologic feature of RCM is LV *myocardial or endomyocardial fibrosis* of uncertain pathogenesis. Antecedent myocarditis might be a cause, but in some cats, RCM clearly represents a late stage of HCM as it does in human patients. Burmese cats might have a predisposition to this disorder.

Post-mortem lesions in cats with clinical features of RCM are dominated by fibrosis that is patchy, multifocal, or diffuse. The LV cavity is generally normal to decreased in size with variable but generally unimpressive hypertrophy, sometimes interspersed with regions of thinning or overt infarction. The latter changes are most evident in the LV free wall or apex. Prominent endocardial or papillary muscle fibrosis might be evident with extreme endocardial fibrotic scarring in some cases (endocardial form). Large false tendons ("LV moderator bands") have been observed (but might be a nonspecific reaction in a diseased left ventricle). A consistent feature of RCM is striking left atrial or biatrial dilation if there is CHF. Histologic lesions include endocardial thickening, endomyocardial fibrosis, myocardial interstitial fibrosis, myocyte hypertrophy, focal myocytolysis and necrosis and arteriosclerosis. Systemic thromboembolism is common and LA and ventricular mural thrombi might be observed.

The clinical pathophysiology of RCM is compatible with a combined diastolic and systolic dysfunction syndrome despite the "normal" fractional shortening in many cats. Increases of venous and atrial pressures, combined with ventricular dysfunction, atrial stiffness, and renal sodium retention, lead to CHF. Most cats with RCM are diagnosed with overt clinical signs

caused by CHF or ATE. Murmurs might not be evident, but loud gallop sounds are the rule, often punctuated by heart rhythm disturbances. The ECG is typically abnormal with wide P-waves, ventricular conduction disturbances, and ectopic complexes common. Atrial fibrillation or atrial standstill might be observed in some cases.

Echocardiography and Doppler studies demonstrate variably: normal or mildly depressed systolic function; regional LV wall dysfunction; mild mitral or tricuspid valvular insufficiency; elevated LA pressures; and impaired LV distensibility with a "restrictive" filling pattern (a nonspecific Doppler sign of CHF). Pulmonary edema, pleural effusion, jugular venous distention, and hepatic congestion are often identified by physical examination and diagnostic imaging. Stasis of blood in a dilated left atrium creates a high risk for atrial thrombi and ATE.

Dilated Cardiomyopathy – This disorder is uncommon today. Taurine deficiency can cause DCM in cats, and this is still observed in cats eating off-brand or some "natural" diets, but most cases are idiopathic or related to diffuse myocarditis. The main postmortem lesions of DCM are left-sided or four-chamber dilatation, generally with necropsy findings of CHF and with no demonstrable congenital, coronary, or valvular heart disease. Histological findings include myocyte loss, prominent interstitial fibrosis, and variable degrees of hypertrophy and myocytolysis or apoptosis. Some cases are characterized by diffuse myocarditis.

The clinical features of DCM in cats are indistinguishable from those of other cardiomyopathies. Heart sounds can be soft owing to impaired contractility or pleural effusion. The principle functional disturbance as shown by echocardiography is marked reduction of LV ejection and shortening fractions, often with mitral and tricuspid regurgitation caused by ventricular dilation and dysfunction. While some cats are detected in the asymptomatic phase, cardiogenic shock, left-sided CHF, or biventricular CHF are the most common presentations. These might be complicated by ATE. Prognosis is poor unless the condition is related to taurine deficiency. Oral taurine supplementation should be administered while awaiting results of a blood taurine test or at a minimum for 2 to 3 months following diagnosis. C-A-F-S-P therapy is prescribed.

Right Ventricular Cardiomyopathy – This condition, sometimes referred to as arrhythmogenic right ventricular cardiomyopathy, has been observed in cats, and the necropsy features have been described. The right ventricle is replaced by fat and fibrous tissue with the consequences of right-sided myocardial failure and right-sided dilatation with tricuspid regurgitation. Right ventricular cardiomyopathy is characterized in most cases by right sided CHF. Atrial standstill or atrial fibrillation might be apparent on the ECG. Ventricular ectopic rhythms are common as well. These cats generally present for clinical signs of pleural effusion, less frequently with concurrent ascites, owing to right-sided CHF that can include development of chylothorax. Sudden death has been reported. Early cases might demonstrate only atrial or ventricular arrhythmias. Diagnosis hinges on echocardiography and exclusion of other predominately right-sided diseases such as atrial septal defect and cor pulmonale. Treatment involves control of CHF and possibly antiarrhythmic therapy.

Reversible or transient ventricular thickening – This term is used to describe cats that typically present with pulmonary edema and other findings of acute left-sided CHF. The LV walls appear mildly-to-moderately thickened, and the cats typically respond to diuresis and management with furosemide, oxygen, and "tincture of time." Follow-up examination (some months later) indicates that the heart is no longer thick, atrial size normalized, cTNI near normal, and medication can be discontinued. Most of these cases of are probably acute myocarditis with infiltration and edema of the ventricular walls. Bartonella has been suspected in a number of cats. Myocarditis can also be associated with infectious diseases including toxoplasmosis, so this should be a consideration before anti-inflammatory therapies are considered. The primary differential diagnosis is a misdiagnosis of CHF in a cat that is also dehydrated and has pseudohypertrophy of the LV walls due to volume depletion. Whether so-called corticosteroid induced cardiomyopathy (typically from Depo-Medrol®) fits into this group of TMT is uncertain.

Nonspecific Cardiomyopathies – The term "Unclassified Cardiomyopathy" is no longer recommended by the ACVIM consensus panel, but *nonspecific cardiomyopathy* (!) is used to describe a myocardial disease of unknown etiology that does not readily fit into one of the above categorizations; there term is generally discouraged. Findings of myocardial form of RCM and NCM are often very similar, and undoubtedly, what one cardiologist might call RCM is classified as NCM by another. Myocardial infarctions and primary atrial diseases might also lead to this diagnosis. Occasionally cats with left atrial dilation, impaired LV diastolic function, but no overt LV myocardial disease are identified (these might be a form of HCM without hypertrophy, a condition recognized in people). The assessment and management of the feline patient with unclassified cardiomyopathy can be "simplified" by describing completely the clinical, imaging, ECG, and biochemical findings evident in the patient and then directing treatments towards managing these abnormalities. Practically, most cases of nonspecific cardiomyopathy present with CHF or ATE and are treated for these problems (see below).

Endomyocarditis – Suppurative endomyocarditis occurs sporadically in cats, mainly younger ones. The cause is unknown and definitive diagnosis requires microscopic examination of the tissues. Some are presented for ventricular arrhythmias, while others develop fulminant heart failure, ATE or RCM. Death during anesthesia is another common scenario. The clinical diagnosis is based on suspicion and exclusion of other diseases. Blood cTnI is generally elevated, but this is not a specific finding for myocarditis, and there is no "gold standard" short of myocardial histology to confirm the diagnosis. No therapies have been shown to be effective in treating myocarditis and patient management is generally supportive, related to identifiable clinical problems.

Hyperthyroid Heart Disease – Thyrotoxicosis causes cardiac hypertrophy related to a hyper-metabolic state, peripheral vasodilation, and increased demands for cardiac output. Increased sympathetic nervous system activity and elevated thyroid hormone levels might stimulate myocardial hypertrophy. In chronic cases of hyperthyroidism, the LV becomes thickened, and concurrent systemic hypertension probably contributes to this in many cases.

Echocardiography typically shows LV hypertrophy, often indistinguishable from mild HCM. Typical findings in advanced cases associated with fluid retention are bi-atrial dilatation with normal to reduced LV ejection fraction. These cats are at risk for CHF, which is often precipitated by the administration of sodium containing fluids. Atenolol can be given to cats that cannot be definitely treated to reduce sympathomimetic signs provided there is no CHF.

Circulatory Overload – This condition is usually observed in cats with comorbidities that predispose to sodium and volume retention (moderate anemia, hyperthyroidism, possibly some cats with primary kidney disease) and follows crystalloid therapy – typically 1.5 to 2x maintenance therapy with Plasmalyte® or lactated Ringer's solution. Frequently these cats have age-related diastolic dysfunction, hypertension, or previously compensated HCM. Echocardiography shows biatrial dilatation and the fluid accumulation is most often in the pleural space (as opposed to cats with moderate to severe HCM where fluid therapy often precipitates pulmonary edema). A helpful sign is to examine the cat for jugular venous distension, which is often present. In most cat, a careful calculation of the sodium intake relative to the actual daily needs demonstrates that the patient is simply "over-hydrated." Reducing fluid intake, using lower-sodium concentrations, and if necessary, diuretic therapy will usually stabilize the situation. A large pleural effusion should be tapped.

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