Feline cardiomyopathies I: HCM update 2019
Feline cardiomyopathies II: the "other" cardiomyopathies and treatment controversies

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Hypertrophic cardiomyopathy (HCM) is the most common acquired heart disease in cats and an important cause of morbidity and mortality. The disease is predominantly characterized by spontaneous and unnecessary hypertrophy of the ventricular myocardium, resulting in diastolic dysfunction and subsequent chamber dilation. Manifestations of HCM vary from subclinical disease that may remain compensated for years to clinical signs of congestive heart failure (CHF), aortic thromboembolism, cardiac arrhythmias, and sudden cardiac death. Accordingly, survival times vary greatly with severity of disease; cats have been reported to survive with occult disease for 1129 to >3617 days, with congestive heart failure for 92-563 days, and with aortic thromboembolism for 1-184 days. [1-3]

Prevalence: In subclinical disease, an auscultable heart murmur may be the first or only sign of cardiac disease. Recent studies have reported a prevalence of heart murmurs in apparently healthy cat populations between 15 and 34%.[3-5] In one study in which cats with no clinical signs of heart disease underwent cardiac auscultation and echocardiogram, the prevalence of HCM was 15.5%, and the positive predictive value of a murmur leading to a diagnosis of HCM was only 31%.[3] This, coupled with recent similar evidence in a UK-based population of cats, suggests that although highly prevalent, HCM may not account for up to two thirds of auscultable murmurs in cats.[6,7]

Consider these three important differentials for an incidentally identified heart murmur in an apparently healthy cat:

- Hypertrophic cardiomyopathy (mild, moderate, or severe)
- Other congenital or acquired disease
- **Physiologic murmur,** particularly *dynamic right ventricular outflow tract obstruction* (DRVOTO), a benign but well recognized physiologic phenomenon

Definitive identification of the source of a murmur requires echocardiography, which likely entails referral to a veterinary cardiologist. A conversation between the referring veterinarian and owner of a cat with an incidentally identified murmur should include the option of referral for and possible outcomes of diagnostic evaluation, the high prevalence of occult heart disease in otherwise healthy cats, and the role of early identification of HCM for proper management and prognosis. The optimal time for referral, (or at least discussing the option of referral with the owner) is upon first identification of a murmur since HCM, like most acquired heart diseases in cats, is irreversible and often progressive.

It is also worth recognizing an important species distinction in cats that differs from what we understand in dogs. HCM –of any severity - can occur without producing an audible heart murmur, particularly if there is no obstruction to left ventricular outflow (which occurs from either hypertrophy of the interventricular septum or from systolic anterior motion of the mitral valve). Moreso than in dogs, heart disease in cats is often left undiagnosed until it is severe enough to cause clinical complications like congestive heart failure, and the variability of audible murmurs is at least one factor in this.

Other auscultable abnormalities of interest include gallop sounds and arrhythmias (the latter of which is covered in a separate lecture). A gallop sound is a third and, specifically, diastolic sound

not commonly heart in normal cats. Lower in frequency than S1 and S2, it can be accentuated by listening with the bell of the stethoscope. It is most commonly identified as S4, a late diastolic sound occurring when the ventricular myocardial walls experience excessive resistance to atrial contraction. This occurs under circumstances of high end diastolic filling pressure and can indicate an imminent predisposition to congestive heart failure, especially in patients undergoing interventions that may "encourage" the onset of CHF – like general anesthesia or intravenous fluid therapy.

Short of an echocardiographic diagnosis, other, more commonly available diagnostics may offer important insight into a cat's cardiac status, specifically:

- Serum biomarkers like NT-proBNP
- Thoracic radiography
- Electrocardiography
- Genetic testing

Biomarkers : NT-proBNP

The natriuretic peptides [Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP)] are synthesized in and released from atrial – and, in the case of BNP, ventricular - myocytes in response to mechanical stretch secondary to volume load. These hormones function to induce natriuresis, diuresis, and mild vasodilation in response to volume overload. Fragments of the precursor molecules (proANP and NT-proBNP) have been measured in cat serum using multiple commercially available human and felines ELISA or RIA kits.[8-12] Elevated atrial pressures, such as in CHF, increase the amount of ANP and BNP and, hence, their precursor molecules in circulation. There is conflicting evidence over the utility of measuring serum proANP in cats, but NT-proBNP has become a widely available and practical diagnostic screening tool.

Studies have demonstrated significant differences in plasma [NT-proBNP] between cats with dyspnea secondary to respiratory disease ([NT-proBNP]<270 pmol/L) and cats with cardiogenic dyspnea ([NT-proBNP]>270 pmol/L).[12,13] Two studies out of the University of California-Davis suggest that plasma [NT-proBNP] is not a useful screening test for HCM because although plasma [NT-proBNP] was significantly higher in severely affected cats versus normal controls, it failed to distinguish those with mild disease.[14,15] Results of a more recent study out of the University of Munich differ greatly, reporting that a plasma concentration >100 pmol/L had a **92.4% sensitivity and a 93.9% specificity** for detecting even mild HCM as compared to normal controls.[16] More recently, a multi-center study compared the [NT-proBNP] in 114 normal, healthy cats with the [NT-proBNP] in 113 cats with occult cardiomyopathy (e.g. no clinical signs of echocardiographically confirmed cardiomyopathy.)[17] In this population of cats, a plasma [NT-proBNP] >46 pmol/L distinguished normal cats from those with occult heart disease with a specificity of 91.2% and a sensitivity of 85.8%. Furthermore, **[NT-proBNP] >99 pmol/L was 100% specific and 70.8% sensitive for identifying affected cats**. The investigators concluded that this biomarker reliably discriminates normal cats from those affected with occult cardiomyopathy and that the degree of increase is associated with particular echocardiographic parameters of disease severity.[17] Clinically speaking, we appreciate that 1) an elevated [NTproBNP] means that heart disease is very likely but 2) does not identify the specific etiology of heart disease nor correlate reliably with disease severity.

The introduction of a point of care (POC) assay (the IDEXX SNAP® Feline Pro-BNP) makes results available more readily which may avoid unnecessary delays in treatment. A positive SNAP test is estimated to correspond to a serum [NT-proBNP] >200 pmol/L. Evaluation by Machen et al. demonstrated a sensitivity of 83% and specificity of 84% for identifying moderate-severe occult cardiomyopathy in cats presenting for evaluation of a murmur, gallop, arrhythmia, or

cardiomegaly.[18]

Plasma [NT-proBNP] has demonstrated clinical utility in differentiating cardiac from non-cardiac causes of dyspnea AND in differentiating normal cats from those with occult cardiomyopathy.

Radiographic and ECG screening for cats with heart murmurs: Generally, radiographic assessment and electrocardiography are specific but insensitive diagnostic tests to identify heart disease in cats. Ventricular hypertrophy specific to HCM does not produce overt radiographic cardiomegaly until/unless it results in enlargement of the left ventricle or left atrium, which often does not occur until the disease is moderate or severe. Many cats with an echocardiographic diagnosis of mild HCM show no radiographic abnormalities in cardiac silhouette size or shape, limiting the ability of radiographs to be useful in early identification of disease.
Some electrocardiographic abnormalities– left anterior fascicular block, ventricular arrhythmias, P wave or QRS prolongation, or third degree AVB – occur in association with structural heart disease, but the absence of these findings does not rule out heart disease.

Genetic testing Over 1400 mutations have been identified in humans with HCM, though a limited number (fewer than a dozen) accounts for more than half of HCM cases. A similar situation may exist in cats, making the potential value of genetic testing attractive, particularly for breeding purposes. In 2005, Meurs et al. described a single point mutation in the gene encoding myosin binding protein C3 (MYBPC3) in a colony of Maine Coon cats.[19] Subsequent work identified a similar mutation in the Ragdoll breed[20] and, currently, both mutations can be identified on commercially available genetic tests (Veterinary Genetics Laboratory at UC Davis; www.vgl.ucdavis.edu and Veterinary Cardiac Genetics Laboratory at NCSU; www.cvm.ncsu.edu/genetics/submit-dna-testing) Prevalence of mutation carriers varies between 22-41.5% of Maine Coon cats depending on geographic distribution of the population studied.[21-22] Not all carriers demonstrate echocardiographic changes consistent with HCM at the time of genetic testing, likely due to age-related penetrance.

Currently:

- Questions arise regarding whether or not mutation carriers should be removed from the breeding pool to mitigate the risk of passing the mutation onto some (heterozygotes) or all (homozygotes) future progeny.
- In the absence of sufficient long term evidence of phenotypic expression among heterozygotes, a genetic test result identifying a cat as a heterozygote is open to discussion between veterinarian and breeder about the cat's potential desirable breeding qualities vs. the risk of propagating a known genetic mutation.
- Mutation carriers should always be evaluated by echocardiography to identify the potential presence and severity of disease and to decide whether intervention is warranted.
- Alternatively, a result indicating that the cat is not a carrier should be interpreted carefully. Specifically, a "negative" result on one of these two tests identifies the cat as a "non-carrier" of one single identified mutation on one gene. There are undoubtedly other yet-unidentified genetic mutations associated with HCM, and breeders and owners alike should be educated that a negative test does not mean the cat does not have or will never develop HCM.

Feline cardiomyopathies II: the "other cardiomyopathies" and treatment controversies

Restrictive/unclassified cardiomyopathy Restrictive cardiomyopathy (RCM) is an acquired cardiomyopathy in domestic cats of largely unidentified aetiology. Reported hypotheses include infectious or immune-mediated endo- or myo-carditis, end-stage ("burn-out") HCM complicated by myocardial failure, or eosinophilia-induced cardiac damage.[23-28] Commonly implicated genetic mutations in humans with RCM have not been identified in cats.[29] The disease is characterized by diastolic dysfunction despite normal myocardial wall diameters and subsequently increased ventricular filling pressures. The decreased compliance of the left ventricle ultimately leads to elevated atrial pressures, which can result in clinical complications of congestive heart failure, thrombus formation and thromboembolic events, or arrhythmias. Because auscultable abnormalities such as audible murmurs, gallop sounds, or arrhythmias occur in a minority of patients (36% in one report), patients with RCM are often not identified until after severe disease results in the onset of these complications.[30] Accordingly, the reported survival time varies but often reflects the later diagnosis: 3 to 1,560 days (median 102) in one study[29] and 1-977 days (median 30 days) in another.[31]

Echocardiographic findings in RCM may include normal LV wall diameters with or without subendocardial hyperechogenicity (indicating fibrosis), normal to variably increased or decreased LV chamber size with frequently preserved systolic function, biatrial enlargement with or without spontaneous echo contrast or a formed thrombus, and criteria of diastolic dysfunction, including a restrictive filling pattern on pulse-wave Doppler of MV inflows or via tissue Doppler of the LV free wall or IVS or MV annulus.[32,33]

Though less well defined, clinicians generally accept that the term *unclassified (or undetermined) cardiomyopathy* (UCM) is used to describe cases with similar echocardiographic findings but without documented restrictive physiology.[23,24,33] Alternatively, UCM may be used to describe findings when other defined criteria of HCM, RCM, DCM, or ARVC are not met in a cat with clear echocardiographic diastolic +/- systolic dysfunction and atrial enlargement. [23,24]

Dilated cardiomyopathy Diseases of systolic dysfunction are uncommon in cats, specifically since taurine deficiency was associated with reversible myocardial failure in 1987, prompting reformulation of many commercial feline diets to include supplemental taurine.[24,30,34-37] Since that time, systolic dysfunction in cats is more commonly linked to idiopathic dilated cardiomyopathy, tachycardia-induced cardiomyopathy, end-stage/"burn-out" HCM, or doxorubicin cardiotoxicosis.[24,38] In Ferasin's retrospective report of 106 cats with cardiomyopathy, DCM was the third most common diagnosis, occurring in 11 cats (10.4% of cases), with HCM and RCM occurring more commonly. [30] A causative genetic mutation has not been identified in cats as it has in Doberman Pinschers with DCM, but genetics may still play a factor in disease.[39,40]

Audible arrhythmias and gallop sounds were previously reported in 79% of cats with DCM, and murmurs of mitral regurgitation were less common.[41] Additional physical exam findings may include muffled or abnormal lung sounds secondary to pleural effusion or pulmonary oedema, abdominal distension secondary to right sided congestive heart failure, pulse deficits associated with arrhythmias, hypodynamic pulses secondary to poor cardiac output, and central retinal lesions.[23,24,35]

A diagnosis of DCM in cats is based on echocardiographic identification of ventricular dilation (increased end-systolic LV diameter, increased E-point to septal separation), normal to thin myocardial wall diameters, low fractional shortening or other measures of impaired systolic function.[32,33,41,42] Additional features may include reduced systolic myocardial velocity on Tissue Doppler, spontaneous echo contrast or thrombus within an enlarged atrium, or AV valve regurgitation secondary to annular dilation.[33,42]

Taurine levels should be measured in cats with echocardiographic findings suggestive of DCM, particularly in cats receiving a diet other than a complete and balanced, commercially available cat food. While endomyocardial samples are most reflective of intracellular myocardial taurine, the need for general anaesthesia and impracticality of endomyocardial biopsy often precludes its use.[24] Instead, taurine concentrations are measured in plasma or whole blood; whole blood concentrations are preferred as these are more likely to include taurine concentrated in platelets and granulocytes and less likely to be affected by the patient's fed or fasted state.[23,24,34,35] Whole blood concentrations < 250 nmol/L are considered deficient and require dietary taurine supplementation (250 mg/cat PO q 12 hours).

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an uncommon primary myocardial disease of cats, accounting for 2-4% of all feline cardiomyopathies.[9,43,33] Paige et al[3] documented ARVC in 1 of 103 apparently healthy cats, while Wilkie et al[45] made a post-mortem diagnosis of ARVC in 4/87 cats suffering sudden/unexpected deaths. As in Boxer dogs and humans, ARVC in cats is characterized by myocyte death and replacement with fibrous or fibrofatty tissue, predominantly within the right ventricle.[44,46] Genetic mutations have been reported in people and Boxers with ARVC but have not been described in cats.[46-50]

In a case series of 12 cats with ARVC, the median age was 7.3 +/- 5.2 years, and no sex or breed predilections were identified.[67] Common presenting complaints may include dyspnoea associated with pleural effusion, ascites, lethargy, anorexia, or collapse. Most cats are diagnosed once they develop signs referable to right sided congestive heart failure.[44] Physical exam may reveal an audible murmur secondary to tricuspid valve regurgitation, a gallop sound or arrhythmia, muffled lung sounds secondary to pleural effusion, jugular distension or pulsation, and/or abdominal distension with or without a palpable fluid wave.

In cats as opposed to dogs, ARVC is an echocardiographic diagnosis. Findings include right ventricular and right atrial dilation with a normal tricuspid valve. Tricuspid dysplasia is the major differential for right heart enlargement. Other variable abnormalities include paradoxical motion of the interventricular septum, tricuspid regurgitation, abnormal trabeculations, or regional dyskinesis or akinesis associated with localized aneurysms, and variable left heart enlargement.[32,33,44]

The arrhythmias occurring in cats with ARVC vary widely and can include any combination of ventricular or supraventricular tachyarrhythmias and variable degrees of AV block.[24,44] Although not strictly an arrhythmia, right bundle branch block may also occur with right ventricular enlargement. Treatment is aimed at controlling rapid arrhythmias and at treating or preventing congestive heart failure or thromboembolism.

Treatment controversies:
Occult disease: atenolol, diltiazem, ACE-inhibitors, clopidogrel
CHF: to use pimo or not to use pimo? That is the question

"Presently, there is no data that establishes a treatment benefit for cats with mild to moderate asymptomatic (occult) cardiomyopathy. Whether therapy reduces disease progression, forestalls morbidity, or improves outcome compared with cats that are not treated at all, lingers as a promise unfulfilled that awaits authentication from evidence-based clinical trials." –PR Fox and KE Schober[51]

Atenolol and diltiazem The proposed therapeutic benefits of beta-blockade in diseases of diastolic dysfuntion include negative chronotropy and negative inotropy leading to decreased myocardial

energy consumption. While recent work has demonstrated a decrease in heart rate, LV outflow tract velocity, and number of ventricular arrhythmias/24 hours in cats receiving atenolol compared to placebo, this has not been shown to correlate to decreased morbidity nor a survival benefit. [52-53] Currently, atenolol (6.25-12.5 mg PO q 12) is empirically reserved for use in obstructive disease or as an anti-arrhythmic. In subclinical disease characterized by an obstruction to left ventricular outflow (secondary to hypertrophy of the interventricular septum or systolic anterior motion of the mitral valve), atenolol is used to limit tachycardia. Tachycardia complicates obstruction, which increases myocardial oxygen demand, and it compromises diastolic filling time. The clinical use of calcium-channel blockers like diltiazem has largely fallen out of favor, probably due to logistical limitations of treatment (i.e. thrice daily dosing).[54-55]
Owners should be educated that once initiated, a dedicated schedule of treatment delivery is essential and abrupt discontinuation of a beta-blocker is potentially harmful to the cat. It is prudent to remember that beta-blockade should never be initiated in acute congestive heart failure or in acute renal failure. Beginning a beta-blocker (because, for example, the heart rate is very rapid) when a cat presents for acute CHF is likely to acutely reduce cardiac output and can readily be fatal. Beta-blockade initiation is always reserved for clinically stable patients. If a cat is already receiving a beta-blocker at the onset of CHF, the dose of the beta-blocker can either be maintained or cut in half while treatment is initiated to resolve critical clinical signs (ie. furosemide for pulmonary edema or thoracocentesis for pleural effusion, etc). The decision to maintain or reduce the dose should be made in light of the cat's clinical stability.

ACE-inhibitors Treatment with ACE inhibitors may be elected prior to the onset of congestive heart failure (clinician-dependent), but evidence to supports its clinical benefit is lacking. Some clinicians empirically initiate enalapril (0.25-0.5 mg/kg PO q 12-24) in cats with left atrial enlargement in an effort to suppress RAAS-mediated sodium and fluid retention and myocardial remodeling. ACE inhibitors should be reduced or discontinued in cats with kidney disease.

Pimobendan Most recently, there is debate over the potential clinical utility of off-label use of **pimobendan** in cats with congestive heart failure secondary to HCM. Pimobendan is a phosphodiesterase III inhibitor characterized by positive inodilator properties. It is labeled for use in dogs with congestive heart failure secondary to myxomatous AV valve disease or dilated cardiomyopathy, and it's been shown to postpone congestive heart failure in asymptomatic dogs with demonstrable cardiomegaly. One case-control study provided provocative evidence of a survival benefit in cats with CHF receiving pimobendan: median survival time of case cats receiving pimobendan was 626 days, whereas median survival time for control cats not receiving pimobendan was 103 days.[56] Two other publications have touted the safety of pimobendan in cats with heart disease but provided more modest survival times (151 and 167 days) without a comparable control group. [57-58]
Most commonly, cats suffer from diseases of diastolic dysfunction and most maintain systolic function. Some of these studies included cats with systolic dysfunction (either primarily- like DCM and ARVC- or as a complication of HCM) but some did not, so the question arose: **how does pimobendan provide a benefit in feline heart disease?** Proposed mechanisms include enhanced contractility in cats with systolic dysfunction, endothelial-dependent vasodilation, and positive lusitropy. Important precautions include a prolonged half-life and higher peak plasma concentration in cats compared to dogs. Currently, the off-label use of pimobendan for cats with heart disease should be reserved for cases where the diagnosis "is confirmed unambiguously with clinical, radiographic and echocardiographic evidence, and especially if there is evidence of decreased left ventricular systolic function."[59]

Clopidogrel Anticoagulation is warranted in cats with evidence of thromboembolic disease or

those with left atrial enlargement, the latter representing the key predisposing factor in the formation of intra-cardiac thrombi.

The anti-platelet drug of choice in cats is clopidogrel at a dose of 18.75mg PO q24 hours. Clopidogrel (Plavix®) irreversibly binds to ADP receptors on the platelet membrane and functions to inhibit platelet aggregation and cross-linking by fibrin. In 2015, the FAT CAT trial (Secondary prevention of cardiogenic arterial thromboembolism in the cat: the double-blind, randomized, positive-controlled feline arterial thromboembolism; clopidogrel vs. aspirin trial) presented evidence that, compared to baby aspirin, clopidogrel resulted in a reduced likelihood of recurrent thromboembolism and a longer median time to recurrence or cardiac death.[60]
One major downside of clopidogrel administration is poor palatability and inappetence in cats receiving it. These side effects may be minimized by having the owner coat each tablet fragment with a thin film of something palatable or hiding the tablet fragment in a tasteless gel capsule.

Anticoagulation for the purpose of mitigating the risk of aortic thromboembolism is indicated in cats with thromboembolism or radiographic or echocardiographic evidence of left atrial enlargement.

Aggressive anticoagulation is recommended in cats with clinical evidence of thromboembolic disease or those with echocardiographically demonstrable left atrial spontaneous contrast or thrombus. Warfarin, unfractionated heparin, and low molecular weight heparin have all been investigated in cats with aortic thromboembolism and all are plausible treatment strategies given that the practitioner is familiar with the indications, doses, and complications of each. Active thrombolytic therapy with recombinant tissue plasminogen activator (rTPA) has been shown to resolve emboli faster than the endogenous thrombolytic system but confers a high risk for reperfusion injury and death. In addition, rTPA is often cost prohibitive. There is newer but yet unsupported interest in specific Factor X inhibitors like rivaroxaban.

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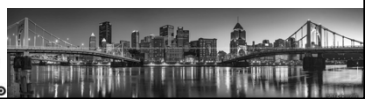
Feline cardiomyopathies I: HCM update 2019

Erin Anderson, VMD, MSc, DACVIM (cardiology)

Pittsburgh Veterinary Cardiology

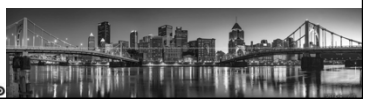


Thank you

- Dr. Ted Robinson and PA Veterinary Medical Association
- Dr. Etienne Côté

No financial disclosures to report

Pittsburgh Veterinary Cardiology



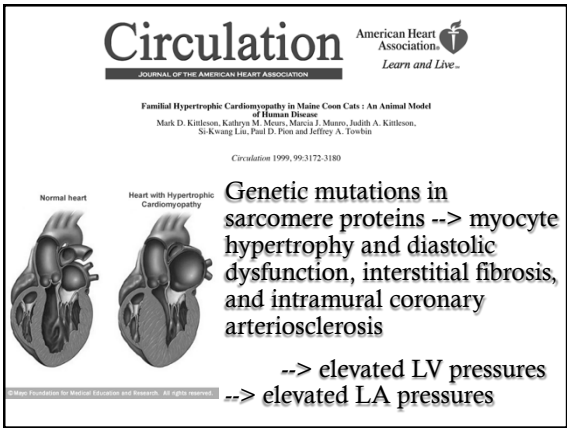
Objectives

HCM

Diagnostic challenge
- Heart murmurs
- Imaging
- Biomarkers: NTproBNP
- Genetic testing

Part II: the "other" cardiomyopathies

Treatment in feline cardiomyopathy



Genetic mutations in sarcomere proteins --> myocyte hypertrophy and diastolic dysfunction, interstitial fibrosis, and intramural coronary arteriosclerosis

--> elevated LV pressures
--> elevated LA pressures

HCM: clinical endpoints

→Congestive heart failure, arrhythmias, aortic thromboembolism

Tremendous range of disease manifestation– from mild /asymptomatic to severe

HCM: survival time

- Subclinical/occult: 1129 to >3617 days
- CHF: 92-563 days
- ATE: 61-184 days

Rush et al, 2002; Atkins et al, 1992; Payne et al, 2010

Many cats harbor undiagnosed heart disease until it results in a clinical crisis/emergency.

Is early disease identification important?

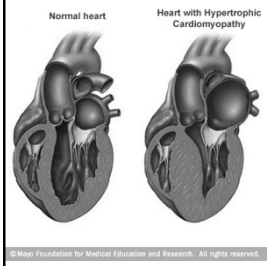
Owner education/expectations

Management of co-morbidities (current or future)- fluid therapy, steroids, anesthesia

Breeding purpose

Treatment…

HCM: murmurs



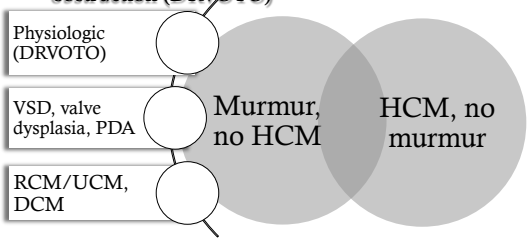
LVOT obstruction

- septal hypertrophy

Systolic anterior motion of the mitral valve (SAM)

+/- mitral regurgitation

Dynamic right ventricular outflow tract obstruction (DRVOTO)



In one study of asymptomatic cats, the positive predictive value of a murmur leading to a diagnosis of HCM was
JAVMA, 2009)

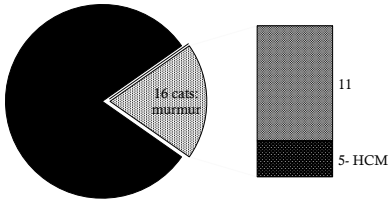
SMALL ANIMALS

Prevalence of cardiomyopathy in apparently healthy cats

Christopher F. Paige, MS, DVM, DACVIM; Jonathan A. Abbott, DVM, DACVIM; François Elvinger, Dr med vet, PhD, DACVPM; R. Lee Pyle, VMD, MS, DACVIM

Hypertrophic cardiomyopathy (HCM) occurs in up to 15.5% of apparently healthy cats (Paige CF et al, *J Am Vet Med Assoc* 2009)

Auscultatory abnormalities in 103 asymptomatic cats (Paige et al, 2009)



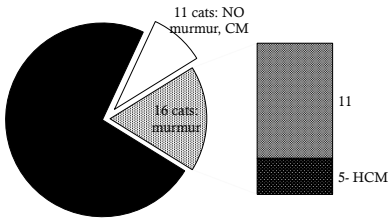
Heart murmurs in cats

Physiologic murmurs in cats due to dynamic right ventricular outflow tract obstruction (DRVOTO)

(Rishniw M and Thomas WP, *J Vet Intern Med*, 2002)

Physiologic murmurs = diagnosis of exclusion via echo. And r/o anemia, fever, hyperthyroidism, dehydration, etc.

Auscultatory abnormalities in 103 asymptomatic cats (Paige et al, 2009)



Murmurs are NOT sensitive indicators of heart dz in cats

J Vet Intern Med 2003;17:73–83

Arterial Thromboembolism in Cats: Acute Crisis in 127 Cases (1992–2001) and Long-Term Management with Low-Dose Aspirin in 24 Cases

Stephanie A. Smith, Anthony H. Tobias, Kristin A. Jacob, Deborah M. Fine, and Pamela L. Grumbles

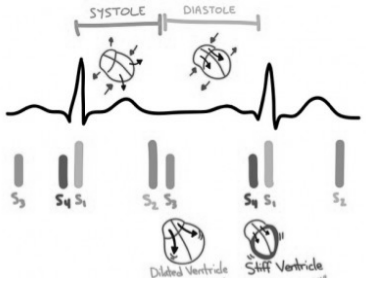
- Murmur only= 25
- Murmur + gallop sound= 9
- Murmur + arrhythmia = 5

39/127 cats with saddle thrombus had murmurs

Murmurs are NOT sensitive indicators of heart dz in cats

Gallop sounds in cats

One of several types of third heart sounds



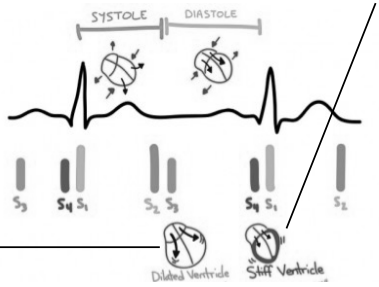
http://sketchymedicine.com/2011/10/heart-sounds

S1=closure of AV valves/start of systole

S2= closure of semilunar valves/end of systole

S4= end-diastolic atrial kick

S3= rapid ventricular filling in early diastole



http://sketchymedicine.com/2011/10/heart-sounds

Gallop sounds in cats

One of several types of third heart sounds

The only low-frequency third heart sound

Gallop sounds in cats

One of several types of third heart sounds

The only low-frequency third heart sound

Therefore, best heard with bell of stethoscope

Gallop sounds in cats

Normal heart sounds
Heart murmurs

Gallop sounds

Gallop sounds in cats

One of several types of third heart sounds

The only low-frequency third heart sound

Therefore, best heard with bell of stethoscope

**Indicates ↑ LV filling pressure **…

CHF is present or imminent

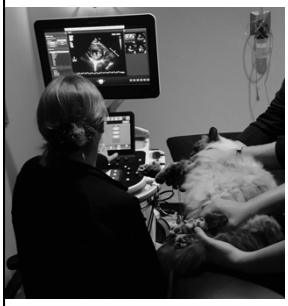
Gallop sounds in cats

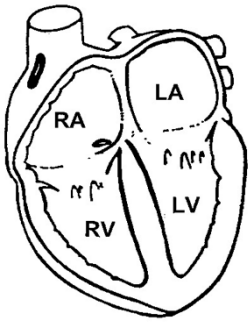
May be "normal" in older cats +/- ↑T4

MOST important in:

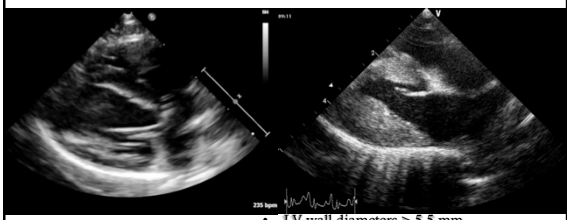
- Symptomatic cats
- New onset gallop- especially in cats on IVF, receiving steroid therapy, or after general anesthesia (situations under which occult heart disease is often "uncovered" in cats)

If murmurs are not sensitive indicators of heart dz in asymptomatic cats, how else might we identify them?





Normal HCM



- LV wall diameters > 5.5 mm
- Evidence of diastolic dysfunction on MV inflows, TDI; abnormal positive strain on speckle tracking imaging
- +/- LVOT obstruction, SAM, false tendons, subendocardial hyperechogenicity
- +/- LA dilation; spontaneous echo contrast

Echocardiography in HCM

Heart rate and hydration status can affect LV measurements

"True" hypertrophy; r/o imposters

- Hyperthyroidism
- Systemic hypertension
- Acromegaly

Cardiac evaluation in cats

Short of an echo, what has high diagnostic yield?

- NT-proBNP
- Thoracic radiographs
- Electrocardiogram
- Genetic testing

Cardiac evaluation in cats

Short of an echo, what has high diagnostic yield?

- NT-proBNP
- Thoracic radiographs
- Electrocardiogram
- Genetic testing

NTproBNP in cats

ProBNP is released from cardiomyocytes under cellular stress/stretch--> BNP works on renal receptors to cause natriuresis and diuresis

Clinical utility in symptomatic patients:

↑[NTproBNP] in cardiogenic > extracardiac dyspnea PR Fox, MA Oyama, C Reynolds, et al. *J Vet Cardiol* 2009 and DJ Connolly, RJSoares Magalhaes, and VL Fuentes,et al. *J Vet Cardiol* 2009.

↑[NTproBNP] in plasma and pleural effusate in cats with pleural effusion caused by CHF than in non-cardiac pleural effusion MJ Hezzell, JE Rush, K Humm, et al. *J Vet Intern Med*, 2016.

NTproBNP in cats

J Vet Intern Med 2011;25:1010–1016

Multicenter Evaluation of Plasma N-Terminal Probrain Natriuretic Peptide (NT-pro BNP) as a Biochemical Screening Test for Asymptomatic (occult) Cardiomyopathy in Cats

P.R. Fox, J.E. Rush, C.A. Reynolds, T.C. DeFrancesco, B.W. Keene, C.E. Atkins, S.G. Gordon, K.E. Schober, J.D. Bonagura, R.L. Stepien, H.B. Kellihan, K.A. MacDonald, L.B. Lehmkuhl, T.P. Nguyenba, N. Sydney Moise, B.K. Lefbom, D.F. Hogan, and M.A. Oyama

Veterinary Clinical Pathology ISSN 0275-6382

ORIGINAL RESEARCH

Utility of measuring plasma N-terminal pro-brain natriuretic peptide in detecting hypertrophic cardiomyopathy and differentiating grades of severity in cats

Gerhard Wess[1], Patricia Daisenberger[1], Monia Mahling[2], Johannes Hirschberger[1], Katrin Hartmann[1]

NTproBNP in asymptomatic cats

- NTproBNP]
  >100pMol/L (93% sens, 94% specific)
  >150pMol/L (100% specific)

  (Wess et al, *J Clin Path,* 2011)

- [NTproBNP]>99pMol/L
  – 100% specific, 71% sensitive

  (Fox et al, *J Vet Intern Med,* 2011)

NTproBNP in asymptomatic cats

[NTproBNP] can be a clinically useful screening test in cats not showing signs of heart disease

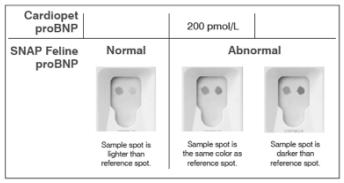
Caution:

Overlap between N controls and mild/moderate dz

Does not identify etiology of heart disease nor guide treatment

Limited knowledge of [NTproBNP] in extracardiac dz (ex. increases in azotemic patients)

IDEXX LABORATORIES SNAP® Feline Pro-BNP



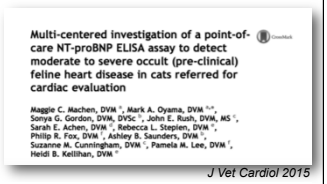
- Positive SNAP = proBNP >200 pmol/L
- Sensitivity = 83%; Specificity = 84%

IDEXX LABORATORIES SNAP® Feline Pro-BNP

More false +'s than false –'s

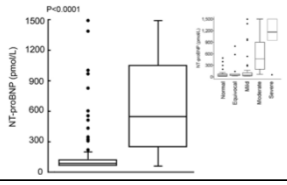
Positive SNAP = proBNP ~ 130 pmol/L

SNAP (neg) reliable for absence of heart dz

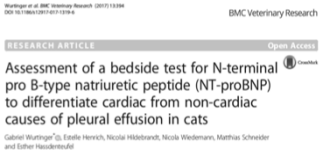

Multi-centered investigation of a point-of-care NT-proBNP ELISA assay to detect moderate to severe occult (pre-clinical) feline heart disease in cats referred for cardiac evaluation

Maggie C. Machen, DVM [1], Mark A. Oyama, DVM [1,2], Sonya G. Gordon, DVM, DVSc [3], John E. Rush, DVM, MS [1], Sarah E. Achen, DVM [1], Rebecca L. Stepien, DVM [1], Philip R. Fox, DVM [1], Ashley B. Saunders, DVM [1], Suzanne M. Cunningham, DVM [1], Pamela M. Lee, DVM [1], Heidi B. Kellihan, DVM [1]

J Vet Cardiol 2015



IDEXX LABORATORIES SNAP® Feline Pro-BNP


BMC Veterinary Research

RESEARCH ARTICLE Open Access

Assessment of a bedside test for N-terminal pro B-type natriuretic peptide (NT-proBNP) to differentiate cardiac from non-cardiac causes of pleural effusion in cats

Gabriel Wurtinger*, Estelle Henrich, Nicolai Hildebrandt, Nicola Wiedemann, Matthias Schneider and Esther Hassdenteufel

20 cats with pleural effusion
  6 CHF
    SNAP-positive on plasma: 6/6 (100%)
  14 non-CHF
    SNAP-positive on plasma: 3/14 (21%)

Conclusion: SNAP Pro-BNP offers rapid information but precision and accuracy are inferior to quantitative NT-proBNP

Cardiac evaluation in cats

Short of an echo, what has high diagnostic yield?

- NT-proBNP
- Thoracic radiographs
- Electrocardiogram
- Genetic testing

Investigating heart dz in cats

Radiographs

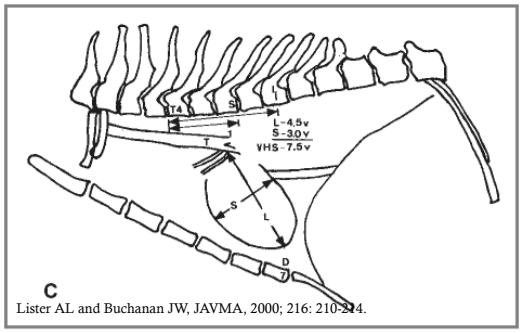
- insensitive for cardiomegaly

J Vet Intern Med 2007;21:709–718

Diagnostic Accuracy of Electrocardiography and Thoracic Radiography in the Assessment of Left Atrial Size in Cats: Comparison with Transthoracic 2-Dimensional Echocardiography

Karsten E. Schober, Imke Maerz, Eberhard Ludewig, and Joshua A. Stern

Results: In cats with LAE, P wave duration and PR interval were prolonged and radiographic LA vertebral heart size (LA-VHS) was increased ($P < .05$). P wave–related indices had low sensitivity (Se; range, 0.12 to 0.60) but high specificity (Sp; range, 0.81 to 1.00) for the prediction of LAE. Radiographic indices had low Se (range, 0.28 to 0.72) and high Sp (range, 0.74 to 0.95) for the prediction of LAE. Correlation analyses identified correlations between LAA and P wave duration ($r = 0.47$, $P = .003$) and LAD and LA-VHS ($r = 0.70$, $P < .001$).



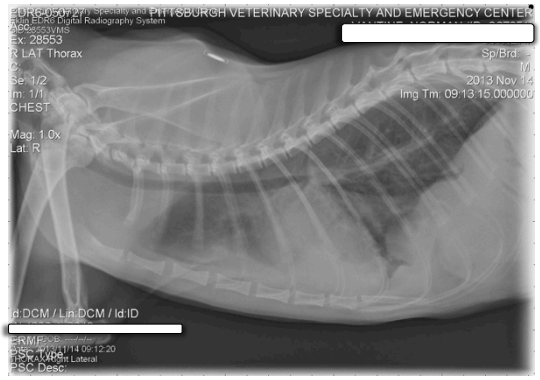
Lister AL and Buchanan JW, JAVMA, 2000; 216: 210-214.

Radiography in cats with heart dz

LVH (as occurs in HCM) is not appreciable on CXR

Generalized cardiomegaly (ie. RVH + LVH) and/or LA enlargement is appreciated in more advanced dz

MOST important utility for CXR in cats:



Radiography in cats with heart dz

Heart size (N<8.0 on VHS)

Very variable distribution of pulmonary infiltrates with cardiogenic pulmonary edema

Only ~ 70% have overt venous distention

Pleural effusion → parenchymal consolidation (creates an interstitial-looking pattern)

Cardiac evaluation in cats

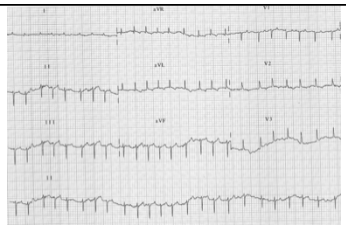
Short of an echo, what has high diagnostic yield?

- NT-proBNP
- Thoracic radiographs
- Electrocardiogram
- Genetic testing

Investigating heart dz in cats

Electrocardiography (ECG)

- Also insensitive = not good screening tool
- Specific
  - Ventricular arrhythmias
  - Left axis deviation (or left anterior fascicular block pattern)
  - QRS duration > 0.04 seconds: 6/6 cats with HCM and 2/17 normal cats [Kvart & Stromberg, ACVIM 2015 (abstract)]



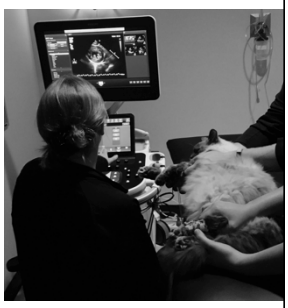
Left anterior fascicular (LAFB) pattern= partial left bundle branch block

QRS complexes are negative in leads II, III, and aVF

QRS complexes are positive in leads I, aVL, and aVR

LAFB may be associated with HCM

Echo remains the gold standard for the specific diagnosis of cardiomyopathy in cats



Cardiac evaluation in cats

Short of an echo, what has high diagnostic yield?

- NT-proBNP
- Thoracic radiographs
- Electrocardiogram
- Genetic testing

HCM: genetic testing

www.catteries.org.uk/MaineCoon.html

www.catspictures.net/2008/08/ragdoll-cats.html

- Myosin binding protein complex 3 (MYPBC3) mutation
- Testing through UCDavis and NCSU

HCM: Genetic testing

- Prevalence in Maine Coons 22-41%
- Breeding consequences

netpetcat.com/tag/maine-coon-pictures

HCM: genetic testing

+ result does not = HCM

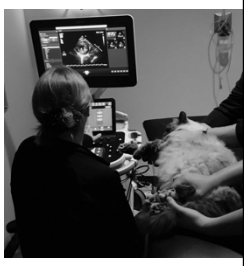
- result = lacking one known mutation, HCM is still possible

- Recommend echocardiogram
- Encourage reporting to breeder
- To remove or not to remove from breeding pool….

Summary

HCM is prevalent in domestic cats and can be difficult to identify early due to the insensitivity of murmurs and many common diagnostic tests.

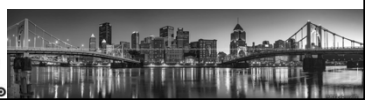
ECHO remains the gold standard for diagnosis, but biomarkers, radiographs, and ECG have a role in evaluation, provided we understand their limitations.



Feline cardiomyopathies II: The "other" cardiomyopathies and treatment controversies

Erin Anderson, VMD, MSc, DACVIM (cardiology)

Pittsburgh Veterinary Cardiology

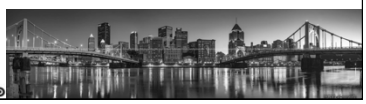


Thank you

- Madrid Small Animal Veterinary Association and VetMadrid 2019 XXXVI Annual Congress- Dr. Susana Garcia Peréz de Ayala, Jaime Diaz, Blanca Seara Millán
- Dr. Etienne Côté

No financial disclosures to report

Pittsburgh Veterinary Cardiology



Objectives

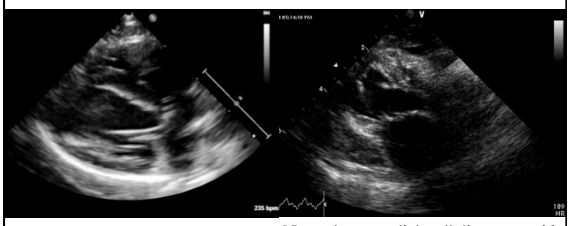
The "other" cardiomyopathies
- Restrictive/unclassified
- Dilated
- Right ventricular arrhythmogenic

Treatment
- Subclinical dz: ACEI, atenolol, clopidogrel
- Decompensated dz

Heart disease in cats

The "other" cardiomyopathies
- Hypertrophic
- Restrictive/unclassified

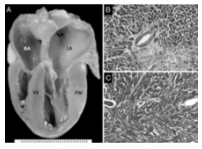
Normal RCM/UCM



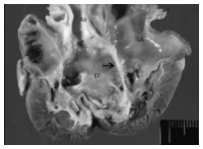
- Normal myocardial wall diameters with often biatrial enlargement
- Evidence of diastolic dysfunction on MV inflows, TDI; abnormal positive strain on speckle tracking imaging

Restrictive/unclassified cardiomyopathy

- Interstitial and/or endocardial fibrosis
- "unclassified" used to denote the addition of systolic dysfunction or a heart so diseased, the primary insult is not recognizeable
- Often diagnosed only after the onset of clinical complications (ATE, CHF, arrhythmias)
  - Only ~1/3 of cases present with audible abnormality (murmur, gallop, arrhythmia)



Fox et al, Cardiovasc Path 2014



Côté, MacDonald, Meurs, Sleeper 2011

Restrictive/unclassified cardiomyopathy

- Common clinical complications:

  CHF

  ATE

  arrhythmias (afib, PVCs, 3rd degree AVB). Kimura Y, Fukushima R, Hirakawa A, et al., *J Vet Med Sci,* 2016.

- Reported survival times vary greatly:
  - 3 - 1,560 days (median 102) *Basson C, Thiene G, Maron BJ. Cardiovasc Path 2014*
  - 1-977 days (median 30) *Kimura Y, Fukushima R, Hirakawa A, et al., J Vet Med Sci, 2016.*

Heart disease in cats

The "other" cardiomyopathies

- Hypertrophic
- Restrictive/unclassified
- Dilated

Dilated cardiomyopathy

Reversible myocardial failure associated with taurine deficiency in 1987

- taurine can still- and should – be measured, esp. if cat is receiving a non-traditional diet

Idiopathic

End-stage/"burn-out" HCM

Doxorubicin cardiotoxicosis

Genetic?

Dilated cardiomyopathy

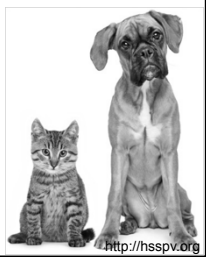
79% of cats in one study had either an audible gallop or arrhythmia, less commonly a murmur

Helinski C, et al. J Vet Intern Med, 1991.

Heart disease in cats

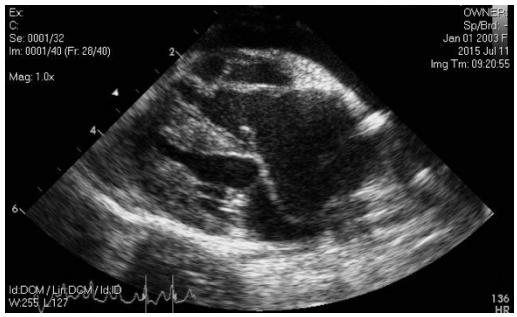
The "other" cardiomyopathies

- Hypertrophic
- Restrictive/"unclassified"
- Dilated
- Arrhythmogenic RV (echo dx, not the case with dogs)



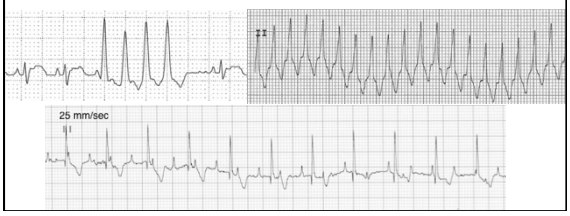
Arrhythmogenic RV cardiomyopathy

- myocyte death and replacement with fibrous or fibrofatty tissue, predominantly within the
- dogs
- In contrast to dogs, ARVC in cats has distinct echo findings



Arrhythmogenic RV cardiomyopathy

-
- Arrhythmias can vary widely



Is early disease identification important?

Owner education/expectations

Management of co-morbidities (current or future)

Breeding purpose

Treatment…

Feline cardiomyopathies: treatment and controversies

"Presently, there is no data that establishes a treatment benefit for cats with mild to moderate asymptomatic (occult) cardiomyopathy. Whether therapy reduces disease progression, forestalls morbidity, or improves outcome compared with cats that are not treated at all, lingers as a promise unfulfilled that awaits authentication from evidence-based clinical trials."

-PR Fox, *J Vet Cardiol*, 2015

Feline cardiomyopathies: treatment and controversies

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Feline cardiomyopathies: treatment and controversies

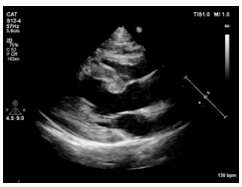
Compensated/occult disease

- beta-blockers
- diltiazem
- ace inhibitors
- anti-platelet drugs

Decompensated disease

Case study

9 yo DSH P/C incidentally identified heart murmur on routine annual exam. Investigate before anesthesia for dental



CBC/CHEM/T4/BP all WNL

Echo: mild HCM, no LAE

Feline cardiomyopathies: treatment and controversies

Compensated/occult disease

- beta-blockers
- diltiazem
- ace inhibitors
- anti-platelet drugs

Decompensated disease

Atenolol for occult HCM in cats

Theory behind beta-blockade in HCM

Negative chronotrope and negative inotrope→ therefore decreases myocardial energy consumption

- Less arrhythmogenesis
- Less fibrosis

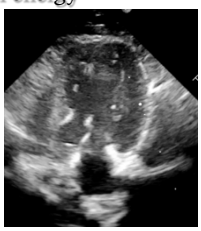
Atenolol for occult HCM in cats

Theory behind beta-blockade in HCM

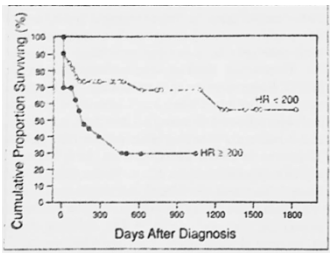
Negative chronotrope and negative inotrope→ therefore decreases myocardial energy consumption

- Less arrhythmogenesis
- Less fibrosis

Reduces LV outflow tract obstruction



Atenolol for occult HCM in cats



Atkins et al, JAVMA 1992

Atenolol for occult HCM in cats

Do these effects prolong survival in cats with preclinical ("asymptomatic") hypertrophic cardiomyopathy?

Atenolol for occult HCM in cats

Do these effects prolong survival in cats with preclinical ("asymptomatic") hypertrophic cardiomyopathy?

In 17 cats with occult HCM, atenolol 6.25-12.5 mg PO q 12:

- ↓HR
- ↓LVOT velocity (obstruction)
- ↓# of PVCs/24 hours

Did not affect systemic BP

Journal of Veterinary Cardiology (2015) 17, S296–S305

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Effect of atenolol on heart rate, arrhythmias, blood pressure, and dynamic left ventricular outflow tract obstruction in cats with subclinical hypertrophic cardiomyopathy☆

Bethany L. Jackson, DVM*, Darcy B. Adin, DVM , Linda B. Lehmkuhl, DVM, MS

Atenolol for occult HCM in cats

Do these effects prolong survival in cats with preclinical ("asymptomatic") hypertrophic cardiomyopathy?

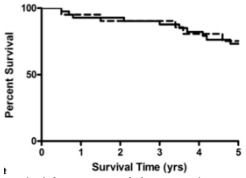
Effect of treatment with atenolol on 5-year survival in cats with preclinical (asymptomatic) hypertrophic cardiomyopathy

Karsten E. Schober, DVM, PhD [a,*], Jillian Zientek, DVM [a], Xiaobai Li, PhD [b], Virginia Luis Fuentes, VetMB, PhD [a,c], John D. Bonagura, DVM, MS [a]

Elsevier, 2014

Atenolol for occult HCM in cats

- 42 HCM cats and 21 normal control cats
- 5-year follow-up
  - All-cause mortality
  - Cardiac mortality



Conclusion

No convincing benefit of atenolol in cats with occult HCM – especially if tx could be detrimental (noncompliant cat or owner)

Possible benefit in subgroups (obstructive disease)

Diltiazem in cats with CHF

Theory behind calcium-channel blockers in HCM

- Negative chronotrope and negative inotrope→ therefore decreases myocardial energy consumption

Evaluation of the Calcium Channel-Blocking Agents Diltiazem and Verapamil for Treatment of Feline Hypertrophic Cardiomyopathy

Janice M. Bright, MS, DVM, A. Lynelle Golden, BS, MS, Rebecca E. Gompf, DVM, MS, Michael A. Walker, DVM, and Robert L. Toal, DVM, MS

J Vet Intern Med, 1991

Diltiazem in cats with CHF

Controlled prospective trial

-
- Diltiazem vs. verapamil vs propranolol PO

Diltiazem

- Was well tolerated
- Decreased median LA diameter to normal
- Improved echo parameters of diastolic function
- 12/17 cats receiving diltiazem no longer needed furosemide 48-72 hours after starting treatment

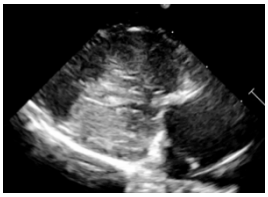
Diltiazem in cats with CHF

Caveats

- Results were never duplicated nor investigated in occult disease
- Logistical challenges: q 8 dosing

Case study

9 yo DSH P/C incidentally identified heart murmur on routine annual exam. Investigate before anesthesia for dental



CBC/CHEM/T4/BP all WNL

Echo: moderate HCM with LA dilation

Feline cardiomyopathies: treatment and controversies

Compensated/occult disease

- beta-blockers
- diltiazem
- ace inhibitors
- anti-platelet drugs

Decompensated disease

ACE inhibition for occult HCM in cats

Theory behind ACE inhibitors in HCM:

Reduction in RAAS-mediated

Na+ and fluid retention

Myocardial remodeling (hypetrophy, fibrosis)

ACE inhibition for occult HCM in cats

In Maine Coon cats with HCM, ramipril treatment over 1 year suppressed plasma ACE activity by 97% compared to placebo but did not result in decreased LV mass as evaluated on cardiac MRI.

J Vet Intern Med 2006;20:1093–1105

The Effect of Ramipril on Left Ventricular Mass, Myocardial Fibrosis, Diastolic Function, and Plasma Neurohormones in Maine Coon Cats with Familial Hypertrophic Cardiomyopathy without Heart Failure

Kristin A. MacDonald, Mark D. Kittleson, Richard F. Larson, Philip Kass, Tyler Klose, and Erik R. Wisner

ACE inhibition for occult HCM in cats

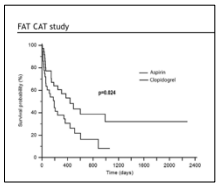
Some cardiologists still consider empiric use of an ACE inhibitor in cats with LA dilation IF AND ONLY IF clinical status, renal function, and systemic BP are and remain WNL.

Use of anti-platelet drugs for occult HCM in cats

Secondary prevention of cardiogenic arterial thromboembolism in the cat: the double-blind, randomized, positive-controlled feline arterial thromboembolism; clopidogrel vs. aspirin trial (FAT CAT)

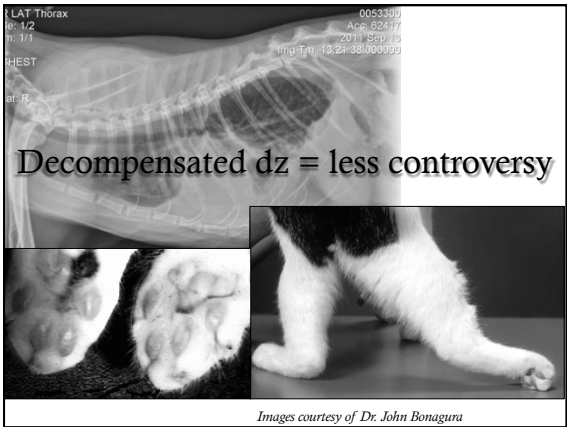
Daniel F. Hogan, DVM [a,*], Philip R. Fox, DVM, MS [b], Kristin Jacob, DVM [c], Bruce Keene, DVM, MS [d], Nancy J. Laste, DVM [e], Steven Rosenthal, DVM [c], Kimberly Sederquist, RVT, VTS-Cardiology [f], Hsin-Yi Weng, BVM, MPH, PhD [g]

J Vet Cardiol 2015



Clopidogrel 18.75 mg PO q 24 : median 443 days to recurrent ATE

Aspirin 81 mg PO q 72: median 192 days to recurrent ATE



Images courtesy of Dr. John Bonagura

Treating symptomatic cardiomyopathy in cats

Congestive heart failure

- Furosemide 1-2 mg/kg PO q 12
- ACEI 0.25-0.5 mg/kg PO q12-24
- Clopidogrel 18.75 mg/cat PO q24
- Spironolactone may be beneficial in some cases
  - ~ monitor for facial pruritus/ulceration

Treating symptomatic cardiomyopathy in cats

Congestive heart failure

Is pimobendan appropriate?

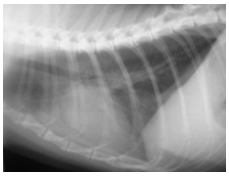
SMALL ANIMALS

Case-control study of the effects of pimobendan on survival time in cats with hypertrophic cardiomyopathy and congestive heart failure

Yamir Reina-Doreste, DVM; Joshua A. Stern, DVM, PhD; Bruce W. Keene, DVM, MS; Sandra P. Tou, DVM; Clarke E. Atkins, DVM, MS; Teresa C. DeFrancesco, DVM; Marisa K. Ames, DVM; Timothy E. Hodge, DVM; Kathryn M. Meurs, DVM, PhD

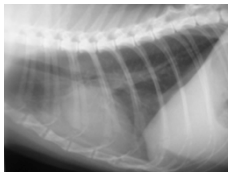
J Am Vet Med Assoc 2014

Pimobendan in cats with CHF



Furosemide + ACEI:

Median survival = 103 days



Furosemide + ACEI + pimobendan:

Median survival = 626 days

Treating symptomatic cardiomyopathy in cats

Congestive heart failure

Is pimobendan appropriate?

Potential benefits

- Improves systolic function
- May have positive lusitropic properties
- Provides vasodilation
- +/- anti-platelet properties

Treating symptomatic cardiomyopathy in cats

Congestive heart failure

Is pimobendan appropriate?

Median survival time = 151-167 days

Journal of Veterinary Cardiology (2011) 13, 251–260

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Journal of Veterinary Cardiology

Use of pimobendan in 170 cats (2006–2010)☆

John M. MacGregor, DVM [a,b,*], John E. Rush, DVM, MS [c], Nancy J. Laste, DVM [d], Rebecca L. Malakoff, DVM [d], Suzanne M. Cunningham, DVM [c], Natalie Aronow, DVM [d,e], Daniel J. Hall, VMD [c], Justin Williams, DVM [d], Lori L. Price, DVM [d]

Effect of oral administration of pimobendan in cats with heart failure

SMALL ANIMALS/ CLINICAL

Sonya G. Gordon, DVM, DVSc, DACVIM; Ashley B. Saunders, DVM, DACVIM; Risa M. Roland, DVM, DACVIM; Randolph L. Winter, DVM; Lori Drourr, DVM, DACVIM; Sarah E. Achen, DVM, DACVIM; Crystal D. Hariu, DVM, DACVIM; Ryan C. Fries, DVM; May M. Boggess, PhD; Matthew W. Miller, DVM, MS, DACVIM

J Am Vet Med Assoc 2012;241:89–94

HCM: survival time

- Subclinical/occult: 1129 to >3617 days
- CHF: 92-563 days
- ATE: 61-184 days

Rush et al, 2002; Atkins et al, 1992; Payne et al, 2010

Treating symptomatic cardiomyopathy in cats

Congestive heart failure

Is pimobendan appropriate?

Caveats:

- Off label use
- Pharmacokinetics: caution in cats
  - Half-life 2.5 times longer than in dogs
  - Peak plasma pimobendan concentration 9 times higher than in dogs
- Theoretically contraindicated with obstructive dz
- Seemingly few appropriate candidates

Treating symptomatic cardiomyopathy in cats

Congestive heart failure

Is pimobendan appropriate?

Maybe most appropriate in advanced or refractory disease

"reserved for cases where the diagnosis is confirmed unambiguously with clinical, radiographic, and echocardiographic evidence, and especially if there is evidence of decreased LV systolic function." –E. Cote

CARDIORENAL SYNDROME

How revisiting physiologic associations between cardiac and renal function can improve the medical management of congestive heart failure in dogs and cats

Erin Anderson, VMD, MSc, DACVIM (cardiology)
Pittsburgh Veterinary Cardiology

Proposed definition of **cardiorenal syndrome (CRS):** scenario in which the primary disorder of 1 of these 2 organs results in secondary dysfunction or injury to the other (Ronco, *et al.*, 2008)

Type 1 CRS: acute worsening of cardiac function → **acute** kidney injury (AKI)

Proposed mechanisms:

- Acutely decreased cardiac output -> decreased glomerular filtration rate (GFR) and tissue hypoxia
- Iatrogenic insult from cardiac therapy: diuretic-induced hypovolemia and/or hypotension, renin-angiotensin-aldosterone system (RAAS) blockade
- Neurohormonal signaling leading to renal necrosis/apoptosis and/or resistance to natriuretic peptides (which normally induce sodium and fluid loss through the kidney)

Type 2 CRS: chronic abnormalities in cardiac function → progressive **chronic** kidney disease (CKD)

Proposed mechanisms (similar to type 1):

- reduced renal perfusion and/or passive renal congestion
- neurohormonal abnormalities, including excessive vasoconstrictors (angiotensin, endothelin, epinephrine) and altered sensitivity to or release of vasodilators (natriuretic peptides, nitric oxide)
- Iatrogenic insult from cardiac therapy: diuretic-induced hypovolemia and/or hypotension, RAAS blockade

Type 3 CRS: abrupt and primary worsening of renal function (AKI) → **acute** cardiac dysfunction [congestive heart failure (CHF), arrhythmias, ischemia)

Proposed mechanisms:

- Iatrogenic fluid overload
- Electrolyte derangements contributing to arrhythmias
- Uremia promotes myocardial depressant factors, possible uremic myo- or pericarditis
- Metabolic acidosis -> pulmonary vasoconstriction, negative effect on systolic function, arrhythmogenesis

Type 4 CRS: primary **C**KD → decreased cardiac function and/or increased risk of adverse cardiovascular events

Type 5 CRS: the presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders (sepsis… less likely immune-mediate disease or diabetes)

The etiologies and manifestations of both cardiac and renal disease differ dramatically between humans and veterinary species, as well as between cats and dogs. Therefore, according to Pouchelon *et al.* (2015), a proposed modification for veterinary patients:

Cardiovascular-renal disorders (CvRD): "disease, toxin or drug-induced structural and/or functional

damage to the kidney and/or cardiovascular system, leading to disruption of the normal interactions between these systems, to the ongoing detriment of one or both."

$CvRD_H$: renal disease/dysfunction emanating from a disease involving the cardiovascular system
$CvRD_K$: cardiovascular disease/dysfunction secondary to renal disease
$CvRD_O$: concurrent impairment of both systems caused by concurrent primary cardiovascular and kidney disease or "other" disease processes, including drugs or toxins that affect both systems
These are subclassified as **stable or unstable disease** based on clinical presentation

Clinical challenge because the general tenants of treatment for renal dysfunction (fluid therapy) commonly oppose those of cardiac dysfunction (diuresis). In physiology, pathophysiology, and clinical management, it's critical to appreciate how intimately these systems are entwined.

Let's start at the beginning. The heart serves two vital functions in physiology: 1) receiving unoxygenated blood via venous return and sending it to the lungs for oxygenation and 2) pumping blood to systemic circulation at a rate commensurate with the requirements of the metabolizing tissues.

Cardiac disease interrupts these functions via several mechanisms. Common in our veterinary patients:

- **Volume overload** (chronic degenerative AV valve disease, dilated cardiomyopathy; less commonly shunts or ischemic/infx/toxic myocardial disorders or high output states like thyrotoxicosis or anemia)
- **Pressure overload/ increased resistance to outflow** (subaortic or pulmonic stenosis, systemic hypertension, hypertrophic obstructive cardiomyopathy, pulmonary hypertension, thromboembolism, heartworm disease)
- **Arrhythmic heart disease** [arrhythmogenic RV (Boxer) cardiomyopathy; tachycardia-induced cardiomyopathy, chronic bradyarrhythmias]
- **Diastolic dysfunction or impaired cardiac filling** (hypertrophic or restrictive cardiomyopathy, pericardial effusion w/ cardiac tamponade, constrictive pericarditis)

When any disease ↓ CO, no matter how small (ie. tiny volume of mitral regurgitation at the onset of degenerative valve disease), compensatory mechanisms are in place to **maintain normal cardiac output (CO) and arterial blood pressure (BP**) and limit clinical signs of heart disease:

- Activation of sympathetic nervous system
    - Normalizes cardiac output via increased HR and normalizes BP via vasoconstriction
- Renin-angiotensin-aldosterone system (RAAS)
    - Maintains cardiac output via increased sodium and water retention
    - Peripheral vasoconstriction
    - Increased contractility via increased preload (Frank-Starling law)
    - Activation of inflammatory mediators
- Neurohormonal modulators like natriuretic peptides, arginine vasopressin (aka anti-diuretic hormone), and endothelin-1

Activation of the sympathetic nervous system

In early heart disease, there is a decrease in CO that activates the sympathetic nervous system:

- Loss of inhibitory input from both arterial and cardiopulmonary baroreceptors
- Excitatory reflexes from peripheral chemoreceptors

Withdrawal of parasympathetic tone, activation of sympathetic tone via upregulation of B1 receptors. Increased sympathetic tone also leads to increase in circulating norepinephrine [NE] (increased release from adrenergic nerve endings *and* reduced uptake). Effects:

- increased heart rate, force of myocardial contraction and resultant increase in cardiac output
- loss of heart rate variability (ie. increased HR to maintain CO)
- increased peripheral vascular resistance (PVR)

Sympathetic activation is helpful in the short term, maladaptive in long term and ultimately contributes to congestive heart failure.

Treatment implication: Beta-blockers reduce morbidity and prolong survival time in people with reduced ejection fraction (ie. similar to the reduced systolic function seen in dilated cardiomyopathy.) In our veterinary patients, β-blockers (carvedilol and metoprolol in clinical trials) did not improve echocardiographic or clinical indicators of heart function in dogs with DCM or chronic valve disease (Oyama *et al.,* 2007; Marcondes-Santos *et al.*, 2007). In another study, β-blockade did not improve diagnostic nor clinical progression of DCM or valve disease compared to baseline (Rush *et al.,* 2002). Clinically, we favor beta-blockade in limited circumstances: SAS or PS or hypertrophic obstructive cardiomyopathy where there is physiologic benefit to blunting the effects of tachycardia (though, generally, evidence to support their use is largely lacking) or to slow supraventricular tachyarrhythmias. Importantly, some β-blockers (of note: atenolol and sotalol) are **renally excreted.** Pure beta-blockers like atenolol (sotalol is only *partially* effective against β-receptors) should <u>not</u> be initiated in the setting of acute congestive heart failure or in uremic patients. In a patient receiving atenolol therapy who develops congestive heart failure OR azotemia/uremia, the dose should be halved or gradually tapered and discontinued if clinically appropriate.

<u>Activation of the renin-angiotensin-aldosterone system (RAAS)</u>

Activated by

- Renal hypoperfusion
- Decreased filtered Na^+ reaching the macula densa in distal tubule
- Increased sympathetic stimulation of the kidney

Increased renin release from the juxtaglomerular apparatus → renin cleaves circulating angiotensinogen (made in liver) to make angiotensin I →angiotensin I gets converted to angiotensin II by angiotensin converting enzyme (ACE) in lung and other tissues

- Majority of ACE activity in tissues (90%)
- Rest in soluble form in the interstitium of the heart and vessel wall (10%)

Other ways of forming angiotensin II

- ACE-independent pathways: angiotenin I to II via chymase, kallkrein, and cathepsin G (rationale for using angiotensin receptor blockers instead of ACE-inhibitors)

Effects of angiotensin II

- Ultimately causes vasoconstriction Na and H20 retention to maintain intravascular volume and BP
- Binds to two G-protein coupled receptors AT1 and AT2
    - Vasculature AT1 → causes vasoconstriction, cell growth, aldosterone secretion from adrenal cortex, catecholamine release

    - Myocardium AT2 → causes vasodilation, inhibition of cell growth, natriuresis, bradykinin release (also a vasodilator)
- Sustained expression of angiotensin II is maladaptive
    - Fibrosis of the heart, kidneys, and vasculature
    - Enhances release of NE from sympathetic nerve endings
    - Like chronic upregulation of the SNS, upregulation of RAAS is initially beneficial but eventually maladapative.

Aldosterone- promotes reabsorption of Na^+ in exchange for K^+ in distal nephron

- Effects of aldosterone (in addition to Na^+ and water retention): interstitial fibrosis (renal and myocardial), endothelial dysfunction, inhibition of NE re-uptake

Treatment implication: There is a lot of evidence both supporting and refuting the therapeutic use of ACE inhibitors in various kinds of heart disease. Studies that show therapeutic effects in dogs with symptomatic valve disease (COVE Study Group, 1995; IMPROVE Study Group, 1995; Ettinger *et al.,* 1998) but no reduced risk for future development of congestive heart failure in dogs with asymptomatic disease (Kvart *et al.,* 2002; Atkins *et al.,* 2007) suggest that although the RAAS is activated early in heart disease, its effect is highest relatively later in the disease course. We would ideally institute ACE inhibitor therapy when chronic RAAS upregulation met "the point of diminishing returns."

In these studies, dogs with valve disease or DCM showed substantially improved hemodynamic parameters (like pulmonary capillary wedge pressure) and a reduced heart failure class when enalapril (0.5 mg/kg PO q 12H) was added to standard diuretic therapy. In the BENCH trial, benazepril was shown to have an equally significant effect on longevity in a large series of dogs with CHF (1999). The evidence is less clear in asymptomatic dogs where one study found that treatment with enalapril therapy made no significant difference compared to placebo in the time until the onset of CHF in 229 Cavalier King Charles Spaniels with valve disease (Kvart *et al.,* 2002). Subsequently, the VETPROOF study group showed that in 139 dogs of various breeds with compensated valve disease, enalapril, compared with placebo, did <u>not</u> significantly prolong median CHF-free days compared to placebo (895 vs. 778 days, p = 0.06, respectively). Interestingly, many cardiologists cite this study as evidence to use enalapril in dogs with moderate valve disease because despite the lack of *statistical* significance, the 117 day difference may be of *clinical* significance.

ACE inhibitors are not inherently nephrotoxic, but they alter renal hemodynamics in important ways:

- Decreased angiotensin II production limits the effects of the overactivated RAAS
- Reduced glomerular filtration rate (GFR) via dilation of the efferent arteriole (also reduces proteinuria)
- Reduced systemic vascular resistance (ie. used as anti-hypertensive agents)
- Blunts tissue remodeling/fibrosis in both the kidney and myocardium

<u>Other neurohormonal modulators</u>

Natriuretic peptides

- Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP)
- produced by myocardial cells under stretch/stress, ischemia, or inflammation
- Released as pro-hormones which get cleaved to inactive N-terminal product (NT-proANP, NT-proBNP) and a biologically active C-terminal end (C-ANP, C-BNP)
- C-ANP and C-BNP bind to natriuretic peptide receptor-A in the heart, kidney, vascular smooth muscle, brain and adrenal glands → vasodilation, increased glomerular blood flow and filtration

rate, reduced sodium uptake, natriuresis and diuresis
- Of **diagnostic significance** because elevated serum [NT-proBNP] indicates the presence of structural heart disease and can distinguish between CHF and primary respiratory disease in dyspneic patients
- Importantly, NT-proBNP is **renally excreted** and has been shown to be elevated in azotemic dogs, which may complicate interpretation (Raffan *et al.,* 2009).

Arginine Vasopressin [AVP, also called anti-diuretic hormone (ADH)]
- Osmoreceptors in the portal veins and hypothalamus monitor plasma osmolality → cause AVP release from posterior pituitary when osmolality is high
- Output arm via two main peripheral receptors
    - V1a receptors in vascular smooth muscle elicit vasoconstriction
    - V2 receptors in renal collecting duct responsible for antidiuretic properties via activation of aquaporin-2 channels, resulting in water reabsorption
    - Uncommonly used class of drugs called "vaptans" (conivaptan, tolvaptain) competitively bind these aquaporin channels to cause free fluid excretion. These drugs are not associated with electrolyte abnormalities like other diuretics but have yet to be thoroughly investigated in veterinary patients.

Endothelin 1 (ET-1)
- Produced by vascular endothelial cells in response to shear stress, hypoxia, ATII and AVP
- Binds ET-A receptors on vascular smooth muscle (aorta, kidneys, and heart) to increase intracellular calcium for profound vasoconstriction
- Myocardial ET-A receptors increase contractility
- Binding to ET-B receptors on vascular endothelium → vasoconstriction. ET-B receptors can also mediate release of nitric oxide, a potent vasodilator.

Through all these mechanisms, the heart and kidneys are intricately controlled and highly vascular organs that work in tandem to regulate systemic BP, vascular volume and tone, tissue perfusion and oxygenation, natriuresis and diuresis. It stands to reason, then, that dysfunction of one organ has a high probability of leading to dysfunction of the other.

Clinical applications

Acute congestive heart failure
- Increased venous pressure leading to pulmonary edema, pleural effusion, or ascites
- Radiographic diagnosis – essential to avoid overdiagnosis (ie. many small breed dogs develop murmurs of chronic valve disease and coughing secondary to airway disease- the cough should not reflexively be treated with diuretics). Acute congestive heart failure (diagnosed radiographically) may cause cough but more commonly causes dyspnea.
- Body cavity effusions (pleura, pericardium, the abdomen)- must be diagnostically investigated (fluid analysis and cytology) +/- therapeutically removed. Diuretics will <u>not</u> quickly mobilize this fluid.
- Obtain CBC/CHEM and ideally a UA prior to diuretic therapy. Diuretics impair renal ability to concentrate urine because the renal medullary interstitial fluid concentration of sodium and chloride is reduced, thus reducing the renal medullary osmolarity. This means USG cannot be used to determine pre-renal vs. renal vs. post-renal azotemia in patients on diuretics (also why we don't routinely/chronically check UA with serum renal values in medically treated patients).

Concurrent azotemia requires better characterization via UA, urine culture +/- UP:C, abdominal radiographs +/- ultrasound. Consider the therapeutic – and prognostic- implications of these etiologies:

- CKD (insert patient between rock and hard place)
- Renal, ureteral, cystic calculi (dietary or surgical therapy)
- Pyelonephritis (additional treatment –antibiotics- necessary)
- Thrombus (additional treatment –anticoagulants- necessary)
- Pre-renal (may improve with return of normal appetite or treatment of CHF or with lower maintenance doses of furosemide if azotemia occurs secondary to acute diuresis)
- Hypoperfusion +/- congestion (may improve with treatment of CHF)

In light of recent publications (Hall *et al.,* 2014; Braff *et al.,* 2014; Nabity *et al.*, 2015), we must also now consider the implication of measuring serum dimethylarginine (SDMA) as an early indicator of reduced GFR

- SDMA is a product of protein methylation that is an early and reliable surrogate marker of GFR
- Elevations in serum SDMA (N<14 μg/dL) occur earlier than elevations in serum creatinine in CKD in both cats and dogs
- SDMA is less affected by lean muscle mass than serum creatinine
- SDMA sometimes increases disproportionately over creatinine. An elevated SDMA:creatinine (>10) predicts increased mortality in animals with CKD (Yerramilli *et al*, 2015)
- No current evidence to suggest how this should be used in the management of cardiac drug therapy. Remember that elevated SDMA reflects decreased GFR… and an elevated creatinine is not far behind.

On the horizon: additional, promising biomarkers like urinary clusterin, serum and urinary cystatin B, serum inosine, and urinary NGAL (neutrophil gelatinase-associated lipocalin) are earlier indicators of active kidney injury.

Acute treatment:

- **Supplemental O_2** [in severe cases, PVSEC has the capacity to use high-flow oxygen therapy (positive-end-expiratory pressure exerted via nasal cannulas in a conscious, non-sedate animal) OR positive pressure ventilation)
- **Furosemide** 0.5-4 mg/kg IV q 4-12 hours (lower dose in cats than dogs) or continuous rate infusion @ 0.5-0.66 mg/kg/hr. Goal is to deplete the extracellular fluid volume at a rate that allows adequate time for intravascular refilling from the interstitium, which makes CRIs an attractive option, particularly in renally impaired patients.
- +/- **pimobendan** 0.25 mg/kg PO q 12 H on an empty stomach in dogs with CHF secondary to DCM or chronic valve disease. Off-label, more limited uses (including in cats) based on echocardiographic findings.
- +/- **nitroprusside** CRI 2-5 mcg/kg/min in D5W- potent vasodilator. $$$
- +/- **dobutamine** CRI 2-10 mg/kg/min – positive inotrope. Caution: arrhythmogenic

Chronic treatment:

- **Furosemide** 0.5-2 mg/kg PO q 12 H (lower dose in cats than dogs). Remember the many formulations of this drug to optimize desired dose. Vet form.: 25 and 50 mg tablets. Human form.: 20, 40, 80 mg tablets. 10 mg/ml oral solution. Or compounded.
    - Very short half life (q 6 hours). Avoid SID dosing
    - *Expect* hyponatremia, hypochloremia, isosthenuria, +/- mild BUN elevation. Beware hypokalemia (arrhythmias, muscle weakness/tremors) which may be alleviated with addition of spironolactone (below) or supplementation of K^+ gluconate or K^+ citrate
    - Alternative loop diuretics (torsemide 0.2 mg/kg PO q 12H) or the addition of different

classes of diuretics (hydrochlorothiazide 1 mg/kg PO q24-48 H, spironolactone-below) may become necessary with recurrent or refractory clinical signs. This should be done with cautious attention to renal values and electrolytes and, ideally, under advisement of a veterinary cardiologist.

- **ACE inhibitor** ("any –pril will do"). 0.25-0.5 mg/kg q 12-24 H if systemic BP > 100 mmHg
  - Enalapril exclusively renally excreted, benazepril heavily hepatically metabolized but both have similar renal effects via decreased GFR
- +/- **Pimobendan** 0.25 mg/kg PO q 12 H on empty stomach
- **Spironolactone** 1-2 mg/kg PO q 12-24 H
  - Used to reduce hypokalemia and diuretic resistance (distal nephron hypertrophy), both induced by furosemide
  - Also used to combat "aldosterone-escape": aldosterone formation can occur even in a patient treated with ACE inhibitor d/t ACE-independent pathways of Ang II formation (chymase, kallikrein)
  - NOT a useful diuretic in the absence of furosemide and is NOT preferentially useful in dogs with ascites. This is a common practice myth that likely stems from the proposed benefit of spironolactone in reducing hepatic fibrosis in humans who develop ascites secondary to cirrhosis/portal hypertension.
  - Rare but reported adverse effect of severe facial ulcerative dermatitis in cats – resolves with discontinuation of drug (MacDonald *et al.,* 2007).
- **Dietary modification:** Sufficient, high-quality protein [5g/100kcal (dogs) and 6.5g/100kcal (cats)] and mild-moderate Na^+ restriction (50-90 mg Na^+/100kcal). Prescription diets labeled for cardiac patients may also contain added K^+, Mg^{++}, taurine, carnitine, coenzyme Q10, and antioxidants. Renal diets are appropriate for patients with cardiorenal syndrome, but they have a lower protein content than is desirable for lone CHF.
  - **Omega-3 fatty acids:** 40 mg/kg EPA + 25 mg/kg DHA shown to be anti-arrhythmic and may combat cardiac cachexia (ie. may promote appetite). Also offer anti-inflammatory, anti-fibrotic, and anti-oxidant benefits in the glomerulus and tubules.

Examples of prescription diets that are mildly to moderately sodium restricted:
Feline: Purina® NF, EN; Iams® dry Low Residue, Renal Plus, Weight Loss/Mobility Plus; Royal Canin® LP, Hypoallergenic selected protein, Senior Consult; Hill's® k/d, g/d, i/d, m/d, c/d (multicare products)
Canine: Purina® HA, DRM, OM, UR, ProPlan Performance 30/20 for All Life Stages; Hill's® j/d, k/d, g/d; Taste of the Wild® Pacific Stream Adult, Wetlands; Wellness® Complete Health Dry Adult Lamb and Barley
Sodium content is not always available on labels. It may be necessary for you or a client to contact a representative of the company supplying the food.

Treating CHF in the face of azotemia associated with CKD:

- Reduce diuretics to lowest effective dose and/or discontinue. Obvious risk of recurrent CHF.
- Reduce or discontinue ACE inhibitors in order to improve GFR. This is often my first adjustment since the risk of recurrent CHF is less than with a reduction in diuretics.
- Reduce or discontinue other renally excreted drugs as applicable: beta-blockers, digoxin.
- Provide fluid support as needed if patient is uremic. Keep in mind the discontinuation of diuretics will improve vascular volume even before fluids are administered.
  - *Slowly* rehydrate. Consider 0.45% NaCl to reduce sodium load + 2.5% dextrose to maintain osmolality (otherwise hypoosmolarity of 0.45% NaCl can cause more rapid shift

into extravascular space).
    - Hourly respiratory rate and effort watch as RR>40 may be an early indicator of iatrogenic fluid overload
    - Use enteral and parental routes as applicable. Let the patient eat and drink if they will. Consider a naso-gastric or esophageal tube. SQ fluids are absorbed over a very variable time frame– avoid if possible.
- Provide symptomatic care as needed: anti-emetics, phosphate binders, appetite stimulants.
- Co-administration of fluid therapy and diuretics makes little sense. These therapies are mutually antagonistic. Consider where on the "spectrum of hydration" the patient falls and amend therapy as necessary [ie. if a cat's been receiving 100mls SQ fluids at home everyday for CKD then develops cardiogenic pleural effusion, reduce amount and frequency of fluids rather than continuing same protocol and instituting diuretics. If a dog who's treated for CHF develops azotemia, reduce diuretics before instituting SQ fluid therapy.]

Most importantly, spend time counseling owner about prognosis and expectations. Cardiorenal syndrome presents a substantial challenge for successful clinical management and client acceptance/tolerance. Moreover, it creates multiple different ways for our patients to decline, so aggressive management and frequent monitoring is necessary, but not often successful for very long.

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Cardiorenal syndrome

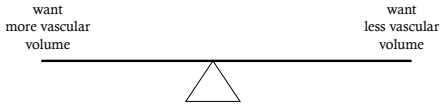
Erin Anderson, VMD, MSc, DACVIM (cardiology)
February 2019

Fundamental clinical problem

- Increasing intravascular volume may improve renal perfusion and glomerular filtration rate (GFR), but increase likelihood of heart failure
- Decreasing intravascular volume may relieve edema, but worsen renal perfusion and GFR

Fundamental clinical problem

- Increasing intravascular volume may improve renal perfusion and glomerular filtration rate GFR, but increase likelihood of heart failure
- Decreasing intravascular volume may relieve edema, but worsen renal perfusion and GFR



Cardiorenal syndrome

disorders of the heart and kidney whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other (Ronco, *et al.*, 2008)

Common and associated with poorer clinical outcomes

Journal of Veterinary Internal Medicine
ACVIM
Open Access

Standard Article
J Vet Intern Med 2016;30:1612–1618

Preliminary Investigation of Cardiovascular–Renal Disorders in Dogs with Chronic Mitral Valve Disease

E. Martinelli, C. Locatelli, S. Bassis, S. Crosara, S. Paltrinieri, P. Scarpa, I. Spalla, AM. Zanaboni, C. Quintavalla, and P. Brambilla

- Prevalence of CKD ↑ in dogs with valve dz than in general population
- Direct correlation between ACVIM class of HF and IRIS stage

- Survival time of dogs with CRS shorter than in dogs with valve dz alone

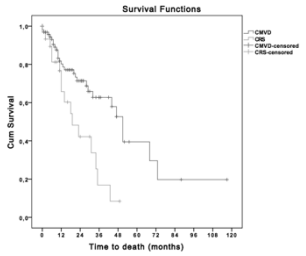


Fig 2. Comparison of survival time between dogs affected by CRS and dogs with CMVD. Blue: dogs affected by CMVD. Green: dogs with CRS. Survival time was statistically different between dogs with CRS versus dogs with CMVD ($P = .002$). End-

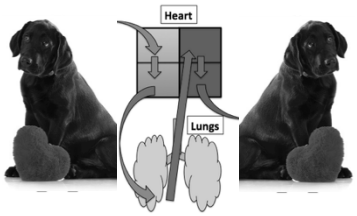
Cardiorenal axis disorders (Pouchelon et al 2015)

"disease, toxin or drug-induced structural and/or functional damage to the kidney and/or cardiovascular system, leading to disruption of the normal interactions between these systems, to the ongoing detriment of one or both"

$CvRD_H$: renal disease/dysfunction emanating from a disease involving the cardiovascular system
$CvRD_K$: cardiovascular disease/dysfunction secondary to renal disease
$CvRD_O$: concurrent impairment of both systems caused by concurrent primary cardiovascular and kidney disease or "other" disease processes, including drugs or toxins that affect both systems

Subclassified by stable or unstable disease based on clinical presentation

Why/how the interdependence?



Two main functions of the heart:
1) To PUMP enough blood to systemic circulation commensurate with needs of metabolizing tissue
2) To receive deoxygenated blood via venous return and pump blood to the lungs for exchange of CO_2 and O_2

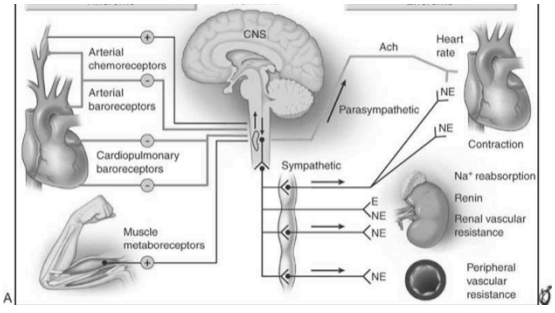
Cardiac pathophysiology

Primary cardiac lesions compromise cardiac output, systemic BP, and O_2 tension.

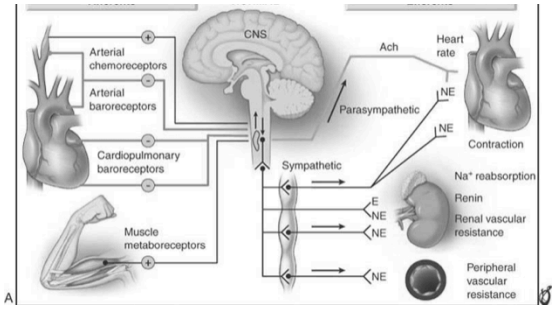
⇩

Compensatory mechanisms are necessary to normalize/ maintain normal systemic BP and O_2 tension
Cardiac output (CO)= stroke volume X heart rate

Sympathetic nervous system (SNS)
Renin-angiotensin-aldosterone system (RAAS)
Natriuretic peptides, arginine vasopressin, endothelin-1



Chronic upregulation of SNS
↓ BP, O_2 tension, $[Na^+]$ trigger an AFFERENT arm that stimulates adrenergic modulation via an EFFERENT arm



↑release of norepinephrine:
- ↑ peripheral vascular resistance -> normalizes BP
- ↑ HR and force of myocardial contraction → normalizes CO

Compensation via SNS

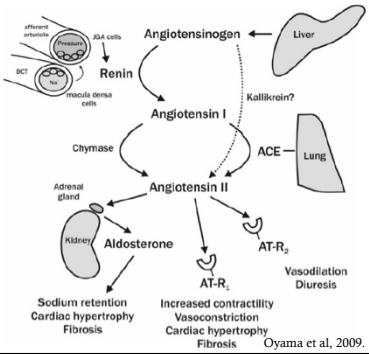
Sympathetic activation helpful in short term…but…

- loss of HR variability
- chronic vasoconstriction and fluid retention
-

The disease process continues unabated and these mechanisms become maladaptive, contributing to cardiac failure (…. And progressive deleterious renal effects).

Compensation via RAAS

Activated by renal hypoperfusion and ↓[Na^+] reaching macula densa in distal tubule



Oyama et al, 2009.

Compensation via RAAS

Like SNS upregulation, RAAS maintains normal BP via vasoconstriction and Na^+ and H_2O retention

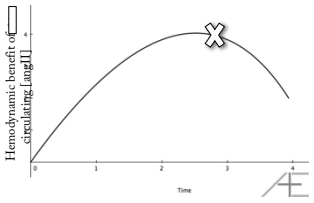
The point of diminishing returns

Chronic upregulation of RAAS

+

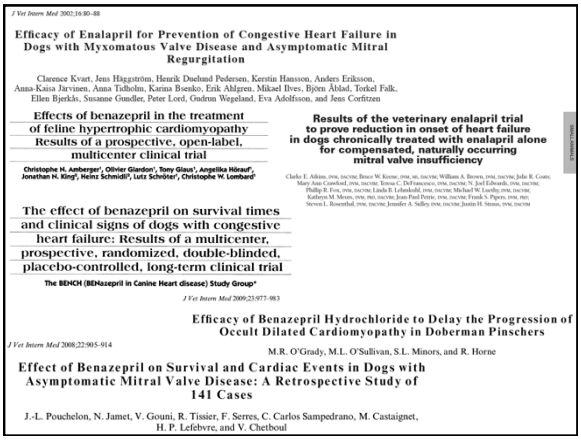
potentiates pre-synaptic release of norepi
fibrosis in myocardium and renal interstitium

Rationale for ACE inhibition



Can we interrupt the overactivated RAAS at the point when it becomes deleterious?

- Na^+ and H_20 retention
- Reduce peripheral vascular resistance /venous pressure
- Decrease risk of progressive myocardial fibrosis



J Vet Intern Med 2002;16:80–88

Efficacy of Enalapril for Prevention of Congestive Heart Failure in Dogs with Myxomatous Valve Disease and Asymptomatic Mitral Regurgitation

Clarence Kvart, Jens Häggström, Henrik Duehund Pedersen, Kerstin Hansson, Anders Eriksson, Anna-Kaisa Järvinen, Anna Tidholm, Karina Bsenko, Erik Ahlgren, Mikael Ilves, Björn Åblad, Torkel Falk, Ellen Bjerkås, Susanne Gundler, Peter Lord, Gudrun Wegeland, Eva Adolfsson, and Jens Corfitzen

Effects of benazepril in the treatment of feline hypertrophic cardiomyopathy Results of a prospective, open-label, multicenter clinical trial

Christophe H. Amberger*, Olivier Glardon†, Tony Glaus‡, Angelika Höraufˆ, Jonathan H. King§, Heinz Schmidli§, Lutz Schröter§, Christophe W. Lombard*

Results of the veterinary enalapril trial to prove reduction in onset of heart failure in dogs chronically treated with enalapril alone for compensated, naturally occurring mitral valve insufficiency

The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure: Results of a multicenter, prospective, randomized, double-blinded, placebo-controlled, long-term clinical trial

The BENCH (BENazepril in Canine Heart disease) Study Group*

J Vet Intern Med 2009;23:977–983

Efficacy of Benazepril Hydrochloride to Delay the Progression of Occult Dilated Cardiomyopathy in Doberman Pinschers

J Vet Intern Med 2008;22:905–914

M.R. O'Grady, M.L. O'Sullivan, S.L. Minors, and R. Horne

Effect of Benazepril on Survival and Cardiac Events in Dogs with Asymptomatic Mitral Valve Disease: A Retrospective Study of 141 Cases

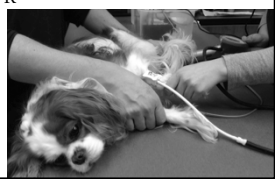
J.-L. Pouchelon, N. Jamet, V. Gouni, R. Tissier, F. Serres, C. Carlos Sampedrano, M. Castaignet, H. P. Lefebvre, and V. Chetboul

Clinical use of ACE inhibitors

Majority of cardiologists initiate use when structural heart disease is moderate (ie. chamber dilation is evident and risk of CHF seems likely in the foreseeable future) or in combination with diuretics in CHF

Evaluate renal function (including UA) and BP before and after starting treatment

Enalapril- entirely renally excreted vs. benazepril – 85% metabolized by the liver; same deleterious effect on GFR



Effect of ACEI on renal fxn

By reducing PVR _> renal hypotension and ↓glomerular capillary pressure (and therefore ↓GFR) can induce or exacerbate azotemia

In humans, successful treatment creates <30% increase in [Cr]

Critical to understand that these drugs have important effects on renal hemodynamics but are not directly nephrotoxic

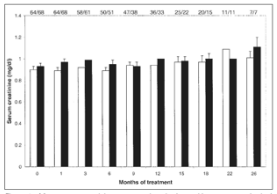


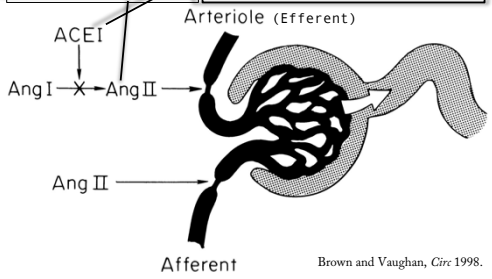
Figure 1—Mean serum creatinine concentrations in dogs with compensated mitral regurgitation treated with enalapril (0.5 mg/kg [0.23 mg/lb], PO, q 24 h; shaded bars) or a placebo (black bars). Numbers above each bar represent number of dogs treated with enalapril/number of dogs treated with the placebo. Error bars represent SEM.

Atkins et al, *Assoc* 2002

Effect of ACEI on renal fxn

AngII normally induces vasoconstriction of the afferent AND efferent arterioles

ACE inhibitors prevent this effect by DILATING the efferent arteriole, reducing the glomerular pressure gradient and therefore reducing glomerular filtration rate



Brown and Vaughan, *Circ* 1998.

Other contributors to neurohormonal model of progressive heart failure

SNS

RAAS

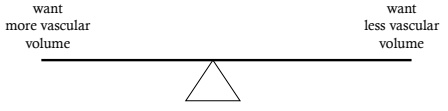
Natriuretic peptides

Arginine vasopressin (aka anti-diuretic hormone)

Endothelin-1

Fundamental clinical problem

- Increasing intravascular volume may improve renal perfusion and GFR, but increase likelihood of heart failure
- Decreasing intravascular volume may relieve edema, but worsen renal perfusion and GFR



Clinical approach to cardiorenal syndrome

Which disorder is predominant?

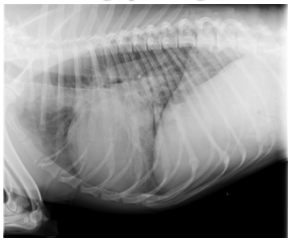
Is this acute or chronic decompensation?

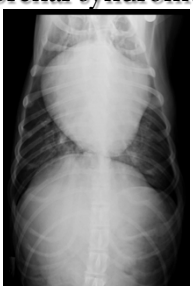
Identification and management of contributing/additional factors

Monitoring and treatment adjustments

Clinical approach to cardiorenal syndrome

1. clinical/radiographic diagnosis





2. Assess renal function before giving diuretics if possible (renal values, electrolytes, USG)

After administration of diuretics, USG cannot differentiate pre-renal vs. renal azotemia

Clinical approach to cardiorenal syndrome

If azotemia is present, consider source:

- Pre-renal (dehydration, poor renal bloodflow associated with CHF) – may eventually improve with medical control of CHF
- Renal (CKD, pyelonephritis, calculi, thrombus) – may require additional or more aggressive therapy
- Post renal (calculi, TCC)

Table 2: International Renal Interest Society Stages of chronic kidney disease in dogs and cats

Stage	Serum creatinine values (mg/dL) Dogs (mg/dL; mmol/L)	Cats (mg/dL; mmol/L)
IRIS CKD Stage 1	<1.4; <125	<1.6; <140
IRIS CKD Stage 2	1.4–2.0; 125–179	1.6–2.8; 140–249
IRIS CKD Stage 3	2.1–5.0; 180–439	2.9–5.0; 250–439
IRIS CKD Stage 4	≥5.0; ≥440	≥5.0; ≥440

Table 3: Classification of proteinuria by urine protein:creatinine ratio*

Classification	Urine protein: creatinine ratio Dogs	Cats
Proteinuric (P)	>0.5	>0.4
Borderline proteinuric (BP)	0.2–0.5	0.2–0.4
Nonproteinuric (NP)	≤0.2	≤0.2

*Based on ACVIM Consensus Statement on Proteinuria.[16]

Table 4: International Renal Interest Society* arterial pressure (AP) stages for dogs and cats

IRIS AP stage	Arterial pressure (AP) Systolic blood pressure	Diastolic blood pressure
Stage 0	<150 mm Hg	<95 mm Hg
Stage I	150–159 mm Hg	95–99 mm Hg
Stage II	160–179 mm Hg	100–119
Stage III	≥180 mm Hg	≥120 mm Hg

*Based on ACVIM Consensus Statement on Hypertension.[2]

Polzin, *Emerg and Crit Care* 2013

J Vet Intern Med 2014;28:1676–1683

Comparison of Serum Concentrations of Symmetric Dimethylarginine and Creatinine as Kidney Function Biomarkers in Cats with Chronic Kidney Disease

J.A. Hall, M. Yerramilli, E. Obare, M. Yerramilli, and D.E. Jewell

- SDMA is a reliable surrogate marker of GFR and increases (N<14 μg/dL) earlier than creatinine does
- SDMA is less affected by lean muscle mass than serum creatinine
- SDMA sometimes increases disproportionately over creatinine. An elevated SDMA:creatinine (>10) predicts increased mortality in animals with CKD (Yerramilli *et al*, 2015)
- No current evidence to suggest how this should be used in the management of cardiac drug therapy. Remember that elevated SDMA reflects decreased GFR… and an elevated creatinine is likely not far behind.

Clinical approach to acute CHF

Supplemental O2

Diuretics

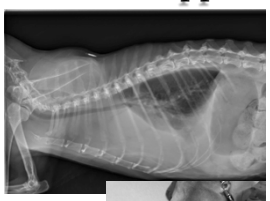
Furosemide 0.5-2 mg/kg IV or IM or PO q 4-12 H in cats

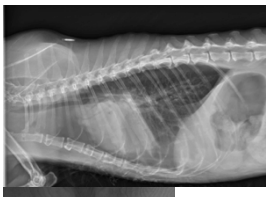
1-4 mg/kg IV or IM or PO q 4-12 H in dogs

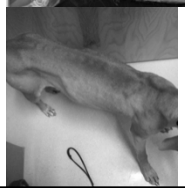
Continuous rate infusions (0.5-0.66 mg/kg/hr) may be preferable in patients with renal dysfunction because they allow depletion of extracellular fluid *slowly and consistently* – which allows adequate time for intravascular filling from interstitial space.

+/- Pimobendan 0.25 mg/kg PO q 12H

Clinical approach to acute CHF







Clinical approach to acute CHF

Let the patient EAT and DRINK- no conscious enteral fluid restrictions

In severe cases, nasogastric tubes can be used to provide enteral water

Clinical approach to chronic CHF

Furosemide 1-2 mg/kg PO q 12 H(dogs)

0.5-1.5 mg/kg PO q 12H (cats)

(* Vet formulations: 12.5 and 50 mg tablets, human formulations: 20, 40, 80 mg tablets, 10 mg/ml oral solution*)

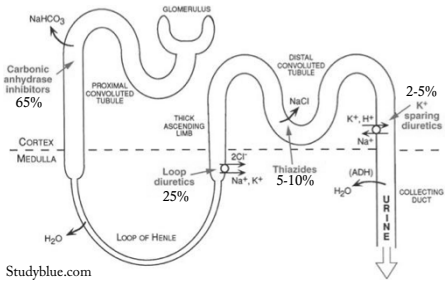
ACE inhibitor 0.25-0.5 mg/kg PO q 12H -24H when eating

+/- pimobendan 0.25 mg/kg PO q 12 H (dogs)

+/- spironolactone 1-2 mg/kg PO q 12 H

+/- clopidogrel 18.75 mg/cat PO q 24 H

Diuretic use in CHF



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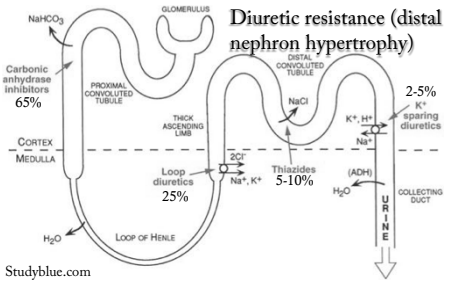
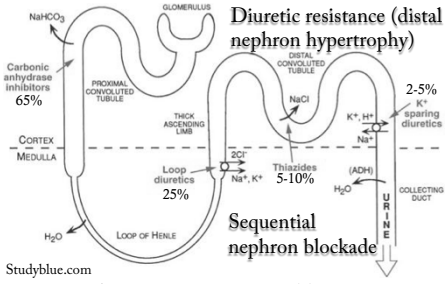
Diuretic use in CHF



Studyblue.com

Loop diuretics: furosemide, torsemide (longer acting, better absorbed, better renal delivery. Dosed ~0.2 mg/kg PO q 12H)

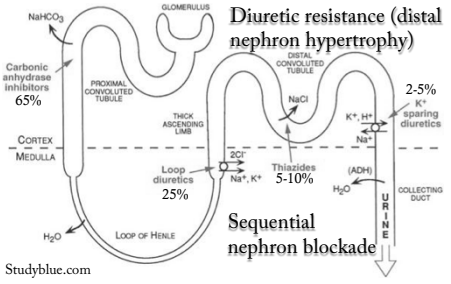
Diuretic use in CHF



Studyblue.com

Thiazide diuretics (hydrochlorothiazide, HCTZ 1mg/kg PO q 24-48 H): *caution* likely to cause or exacerbate azotemia and elyte disturbances, esp. with furosemide

Diuretic use in CHF



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Spironolactone: used to combat diuretic resistance, aldosterone escape, and to reduce lasix-induced hypokalemia