A REVIEW OF DILATED CARDIOMYOPATHY IN DOGS

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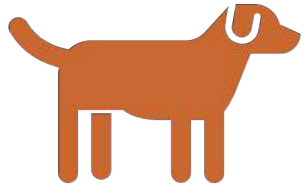
DISCLOSURES:



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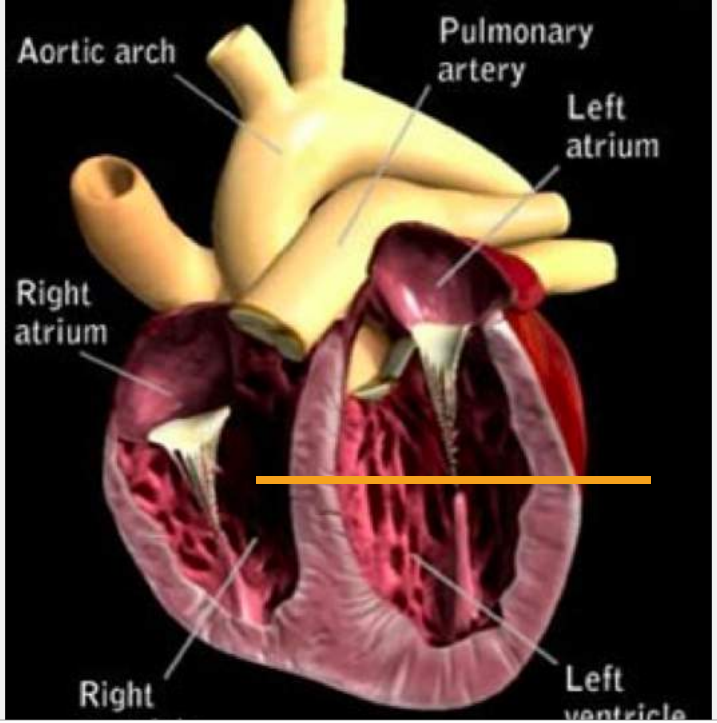
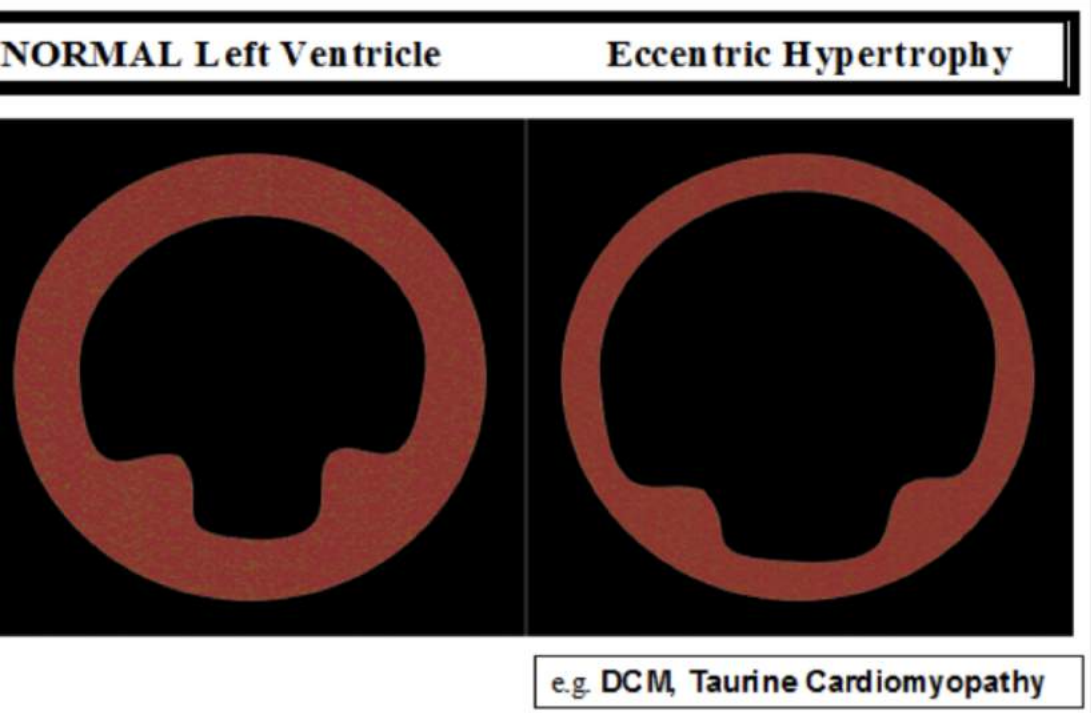
OUTLINE:

- Definition
- Signs
- Incidence
- Causes
- Diagnosis
- Prevention & Treatment
- Recent Reports
- Where to go from here





WHAT IS DILATED CARDIOMYOPATHY (DCM)

- **Cardiomyopathy:**
  - Cardio: Heart
  - Myo: Muscle
  - Pathy: Disease
  - **Primary:** Disease of the heart muscle of unknown etiology
  - **Secondary:** Disease of heart muscle due to toxins, nutritional deficiencies, endocrinopathies and infection
  - **Dilated Cardiomyopathy:** Progressive ventricular dilation and loss of myocardial contractility

THE SIGNS OF DCM:

Occult DCM: No clinical signs

- Increased left ventricle dimensions (dilation)
- +/- increased atrial dimensions
- Decreased ability for the heart to contract
- +/- Ventricular premature contractions (VPCs)
- May last months or years
  - Worsening arrhythmias and progressive heart enlargement

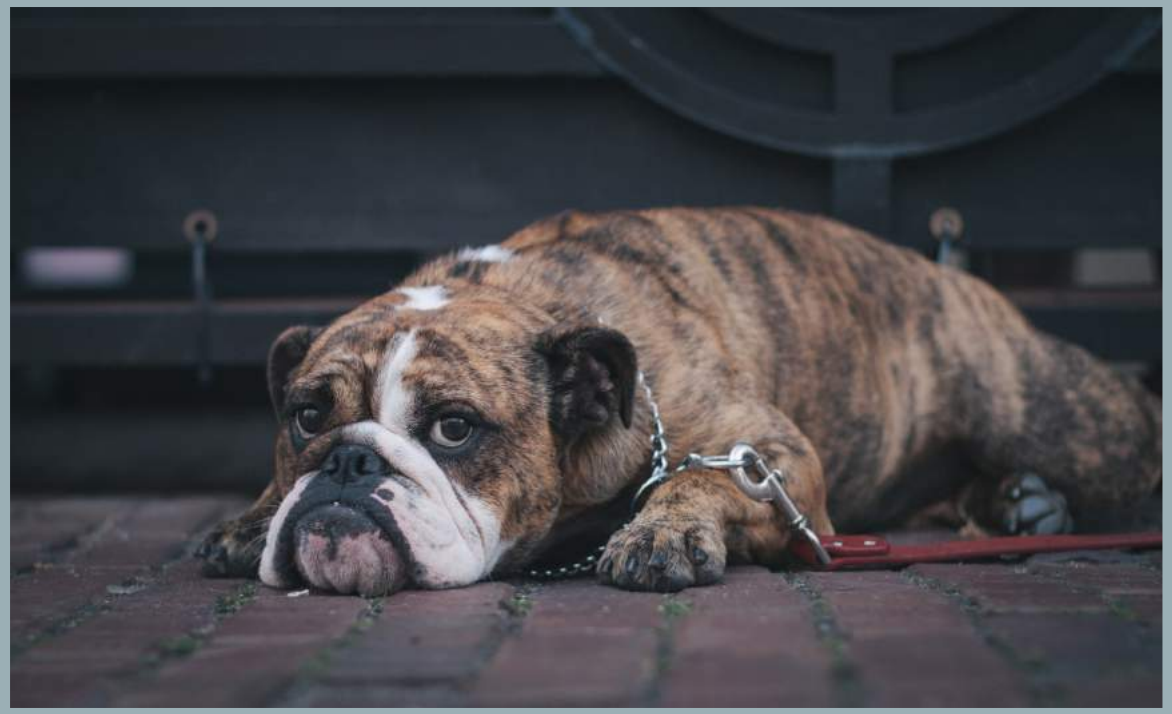
This phase ends with the appearance of first clinical signs

- Sudden death may occur in the occult phase
- About 40% of Dobermans experience sudden death as their first clinical sign

THE SIGNS OF DCM:

Overt Clinical Phase - congestive heart failure, arrhythmias, or both

- Congestive Heart Failure (CHF)
  - Respiratory distress
  - Cough
  - Anorexia
  - Weight loss
- Arrhythmias
  - May be ventricular or supraventricular
  - Syncope: loss of consciousness/collapse
  - Exercise and activity intolerance
- Death due to CHF or sudden death



WHO IS TYPICALLY AFFECTED?

- Canine Cardiomyopathy In: Canine & Feline Cardiology, 5th edition 2016
  - 2-6 dogs are diagnosed with DCM per 600 case referrals
  - 25% Irish Wolfhounds
  - 50% of all male Doberman Pinchers
  - 33% of all female Doberman Pinchers
- Other Reports:
  - Standard Schnauzers
  - Boxers
  - Golden Retrievers
  - Cocker Spaniels
  - Great Danes
  - Newfoundlands
  - Scottish Deerhounds

WHAT CAUSES DCM?

- "An increased understanding of the etiology of both human and canine disease has led to the development of the theory that DCM is the final result of a variety of myocardial insults including viral, nutritional, toxic and genetic." Myocardial Disease: Canine, Veterinary Internal Medicine, 7th Ed. Editors: Ettinger, Feldman
  - Genetics - breed specific inheritance
  - Nutritional Deficiencies - taurine, carnitine
  - Toxins - chemotherapy
  - Endocrine disease - hypothyroidism
  - Infection / Inflammation - myocarditis
  - Arrhythmias - chronic rapid heart rate

GENETICS:

- Dobermans: PDK4 gene
- Boxers: STRN gene (Striation mutation)
  - 30/33 Boxers with DCM
  - 3/33 some other unknown cause (L-carnitine, viral)
- German Shorthaired Pointers: DMD gene
- Great Danes: X-lined likely since males predisposed - specific gene unknown
- Portuguese Water Dog: Autosomal recessive inheritance -specific gene unknown

POTENTIAL NUTRITIONAL CAUSE - TAURINE:

- Sulfur containing amino acid, not incorporated into proteins
- In highest concentrations in cardiac muscle, skeletal muscle, central nervous system, platelets
- Unlike cats, dogs synthesize from **cystine and methionine**
- Mechanism unknown:
  - Modulating tissue calcium and concentration and availability
  - Inactivation of free radicals and protect the heart by changing cellular osmolarity

DIET RELATED DCM: TAURINE

- May occur more commonly due to higher requirements or breed specific metabolic abnormalities
- Diet may also play a role: Applied Veterinary Clinical Nutrition, Nutritional Management of CV Diseases, 2012
  - Very low protein
  - Lamb meal and rice
  - Higher fiber diets have been associated
  - Exact role of diet unknown at this time

POTENTIAL NUTRITIONAL CAUSES – TAURINE, METHIONINE & CYSTINE

- Sanderson. Taurine and Carnitine in Canine Cadiomyopathy, Vet Clin North Amer
  - Earlier studies showed Beagle dogs did not have adverse effects when fed diets devoid of taurine
  - Then in 1989 taurine deficiency related DCM identified in foxes
  - Then plasma taurine assessed in dogs with DCM and mitral valve disease
    - 17% of dogs with DCM had low taurine status and this deficiency was seen in breeds that were not previously considered to be at high risk including American Cocker Spaniels and Golden Retrievers
    - However dog breeds that were considered commonly affected with DCM had taurine concentrations within the reference range.
    - Concluded taurine deficiency unlikely to be playing a major role in pathogenesis

POTENTIAL NUTRITIONAL CAUSE – TAURINE, METHIONINE & CYSTINE

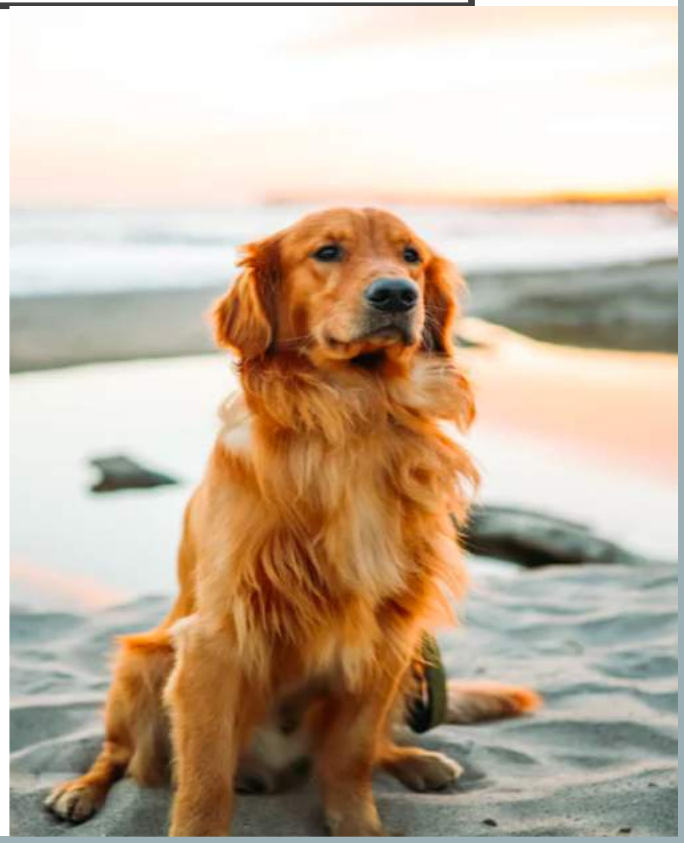
- **Multicenter Spaniel Trial**
  - Cocker Spaniels supplemented with L-carnitine and taurine showed improvement in signs and echocardiogram within 4 months
- **Dogs on protein restricted diet for management of urate bladder stones**
  - DCM: Reversed and lived longer when supplemented with taurine and L-carnitine
- **Taurine deficiency identified in two unrelated dogs fed soybean curd based diet**
  - Devoid of taurine
  - Low in sulfur containing amino acids though met NRC requirements

POTENTIAL NUTRITIONAL CAUSE – TAURINE, METHIONINE & CYSTINE

- **Lamb Meal & Rice**
  - Taurine deficiency in 12 Newfoundlands WITHOUT DCM: improved w/ taurine or diet change
  - 12 large and giant breeds, with DCM, reversed with taurine supplementation
  - 5 related Golden Retrievers diagnosed with taurine deficiency & DCM, 3/5 lamb & rice diet, improved with taurine supplementation, survived > 3 year
  - Low bioavailability of sulfur containing amino acids with these ingredients
  - Rice bran and whole rice products -> fiber to colon & fat -> increase loss of taurine in feces

POTENTIAL NUTRITIONAL CAUSES – TAURINE, METHIONINE & CYSTINE:

- Breeds Predisposed:
  - American Cocker Spaniels
  - Newfoundlands
  - Golden Retrievers
  - Labrador Retrievers
  - Dalmatians
  - English Bulldogs
  - Portuguese Water Dogs



POTENTIAL NUTRITIONAL CAUSES – L-CARNITINE

- Water soluble, vitamin-like molecule
- Synthesized from Lysine & Methionine
- Primarily in cardiac and skeletal muscles
- Heart stores it but can't make it
- Why it's important
  - Heart gets energy from long chain fatty acids
  - In order for those to get into the mitochondria to be used to make energy, L-carnitine has to take it there

POTENTIAL NUTRITIONAL CAUSES - L-CARNITINE

Sanderson. Taurine and Carnitine in Canine Cardiomyopathy, Vet Clin North Amer, Sm Anim Prac

- Carnitine status difficult to assess
- Types of carnitine deficiency in dogs:
  - Plasma deficiency
  - Myopathic deficiency
  - Systemic deficiency
- If plasma carnitine is low, it helps to diagnose deficiency. If it is normal or high, you could still have myopathic deficiency
  - Occurs in 17-60% of dogs with DCM
  - Requires endomyocardial biopsy

POTENTIAL NUTRITIONAL CAUSES– L-CARNITINE

- L-Carnitine deficiency first reported in a family of boxers
- Another report discussed 2 boxers with DCM. One treated with L-carnitine and the other without.
  - Boxer without supplementation had low myocardial carnitine concentration and was elevated in the dog that did receive it
- Cocker Spaniels with DCM: Carnitine and Taurine supplementation helped

POTENTIAL NUTRITIONAL CAUSES: L-CARNITINE

- Is low carnitine the cause or the effect?
  - Carnitine can leak out of damaged heart muscle
  - Unpublished study at University of Minnesota documented 3 cases of carnitine deficiency prior to onset of DCM
    - One was a mini dauchshund which improved **only** with Carnitine supplementation

POTENTIAL NUTRITIONAL CAUSES - OTHER NUTRIENTS

- Thiamine: Deficiency associated with CHF
  - Deficiency in 33% of human patients with DCM
  - Diuretics
- Copper:
  - Mice with induced DCM had improvement cardiac function and pressure overload with supplementation
- Vitamin E and Selenium:
  - Vitamin E decreased with increasing severity in dogs
  - Report of nutritional myopathy (se and vitamin E) in a puppy where LV affected
  - Se deficiency in humans is associated with DCM and reversed with supplementation

NUTRIENT-NUTRIENT INTERACTIONS

- Taurine: Methionine & Cystine
- `Co-Factors:
  - Zinc, choline, copper, thiamine, vitamins E, A, B5, B6 and Selenium
- L-Carnitine: Lysine & Methionine
  - Co-factors:
    - Ascorbic acid. Nicotinamide, B6, iron
- Food Processing: Amino acids and other precursors could be degraded
- Macronutrients:
  - Affect another nutrient's bioavailability
  - Fiber: Inhibits digestibility of protein
    - Decreased sulfur amino acid availability and ability to synthesize taurine
    - Large and medium breeds given beet pulp (KO & Fascetti, 2016)

Equus Magazine

TOXINS:

Cassava and cyanogenic glycosides:

- Cyanide is converted to thiocyanate which requires sulfane sulfur from sulfur containing amino acids (Dolan et al, 2010)
- When the body is detoxifying there is increased demand for sulfur containing amino acids (Tor-Agbidye, et al, 1999)

Goitrogenic foods:

- Spinach, cassava, peas, soybeans, strawberries, sweet potatoes, peaches, pears, broccoli, Brussel sprouts, cabbage, canola, cauliflower, mustard greens, radishes, rapeseed
- Decrease thyroid hormone which is known to be a cause or contributing factor to development of DCM (Bhardwai, 2009)

Chemotherapeutics:

- Doxorubicin

ENDOCRINE

- Hypothyroidism:
  - Thyroid hormone affects contractile and relaxation properties of the heart
  - Thyroid hormone signaling may help to preserve cardiac structures and performance
  - Diastolic and systolic function affected by thyroid hormone
  - Peripheral vasculature affected by thyroid hormone affecting ventricular contractile function
  - Thyroid dysfunction associated with worse prognosis in cardiac patients
  - 33/256 (12.9%) hypothyroid dogs had DCM (Karlapudi SK, Srikala D, Rao T. Vet World, 2012, Vol 5(12):742-747)

MYOCARDITIS

- Inflammation of the myocardium (heart muscle)
- Characterized by acute onset arrhythmias, syncope, and/or congestive heart failure
- Patient may be any breed, sex or age
- Suspect myocarditis in any breed that doesn't typically get DCM
- Troponin is the most sensitive indicator of myocarditis
- Endomyocardial biopsy may definitively diagnose myocarditis but may not identify causative agent.

- **In humans:**
  - Many cases are thought to be viral in origin.
  - An auto-immune component is possible, though not documented in the dog.
  - May spontaneously resolve, or patient may develop viral persistence

DIAGNOSIS:

- Clinical Signs:
  - cough
  - syncope
  - increased respiratory rate/effort
- Physical Exam:
  - Heart murmur
  - Arrhythmia
  - Abdominal fluid
  - Poor pulses +/- deficits
  - Hypotension (low blood pressure)
- Radiographs
  - Early stages may be normal
  - Enlarged heart
  - Evidence of congestive heart failure
  - Abdominal fluid

* Radiographs cannot distinguish between different types of heart disease - many diseases result in similar abnormalities

DIAGNOSIS:

- Electrocardiogram (ECG)
  - may detect arrhythmias (absence does not rule out intermittent arrhythmias)

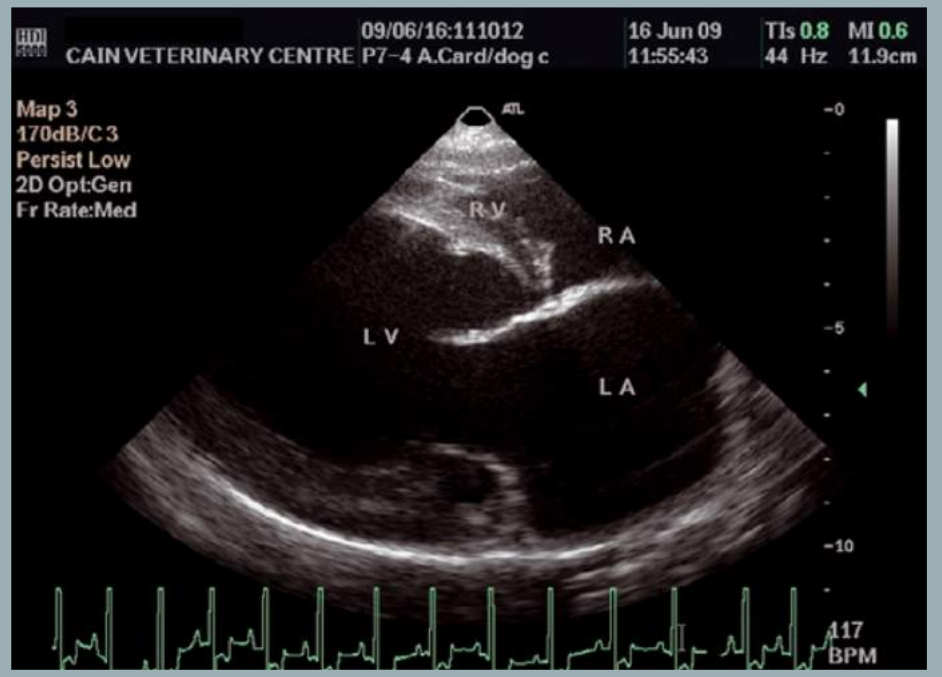
- Cardiac Biomarkers::
  - Cardiac Troponin I: Measures heart cell death (acutely)
  - B-type Naturietic Peptic (NT-proBNP):

    - Released with abnormal stretch/strain on the heart muscle.

      - Sensitive and specific marker of heart disease

      - Does not distinguish between types of heart disease.

- Echocardiogram:
  - Definitive diagnosis
  - Requires specialized equipment and specialized training



Gerrard E, VN TImes, 2013

PREVENTION & TREATMENT:

Prevention unknown at this time – depends on cause

- Screening and early detection and treatment

Occult stage:

- ACE inhibitors: Prolonged time to CHF in Doberman's studied
- Pimobendan : Prolongs life by ⅓ (PROTECT Study)
- L-Carnitine: 1000 mg three times daily (100-200 mg/kg three times daily)
- Taurine: 500 mg twice to three times daily

Congestive Heart Failure

- Pimobendin: Prolonged survival of Dobermans studied from 14 d to 130 days median
- Diuretics
- Omega-3 Fatty acid: Anti-arrythmogenic and helps prevent cachexia
- Low sodium diet

In Recent Reports…..

Dr. Bradley Quest

FACTORS TO CONSIDER:

ASSOCIATIONS VS. CAUSE AND EFFECT

SAMPLING AND SAMPLING BIAS

POTENTIAL NUTRITIONAL CAUSES

RECENT REPORTS:

FDA release July 12, 2018

- 1st mention of investigation, no data shared on #'s of dogs reported to FDA at this time. No data shared on incidence of DCM in overall dog population.
- One 1980's European study suggests 1% of dogs presented to Veterinarians (Fioretti et al, 1988). 1990's Purdue study shows 0.5%dogs presented to referral Veterinary hospitals (Sisson ed. in Ettinger, 1995).
- "The FDA encourages pet owners and veterinary professionals to report cases of ***DCM in dogs suspected of having a link to diet*** by using the electronic Safety Reporting Portal or calling their state's FDA Consumer Complaint Coordinators."
- "The agency has also been in contact with pet food manufacturers to discuss these reports and to help further the investigation." example of manufacturer's contact with FDA:
- April 2018- phone call asking where diets were made
- June 2019- phone call informing of pending FDA update naming companies.

RECENT REPORTS:

FDA release February 29, 2019

- "Between January 1, 2014, and November 30, 2018, the FDA received ***300 reports of DCM*** (294 canine reports, 6 feline reports);…"
- "Collaborating with Chesapeake Veterinary Cardiology Associates (CVCA) to collect case summaries and blood/serum/tissue of dogs diagnosed with DCM…". 14 locations in 4 states.
- Why not other large database Veterinary businesses ie Mars Petcare (Banfield, Blue Pearl, Pet Partners, VCA).?? >2,000 clinics in almost every state. Many with ACVIM diplomats and cardiac ultrasound capabilities.
- "The FDA continues to encourage pet owners and veterinary professionals to report both symptomatic and asymptomatic cases of dogs ***suspected to have DCM connected to diet***…"

RECENT REPORTS:

FDA release & Vet LIRN release June 27, 2019-

560 dogs in this report group that were "diagnosed with DCM"- not sure how? Via med records? Cardiology exams?

As of 4/30/19, FDA reviewed 340 dogs medical records - 202 dx w/ DCM based on dec. ventricular function and cardiac ultrasound. 202/340 = 60%. 61% of these 202 dogs had CHF- suggesting these dogs had even more serious cardiac disease

Of these 202 confirmed DCM dogs:.

1. 15% had chronic valvular degeneration (CVD)- most common heart dz in dogs.
2. 12%- atrial fibrillation. This rhythm is common in large breed dogs with CHF (enlarged heart predisposes).
3. 38%- environmental/food allergy. Symptoms dermatitis, otitis, GI
4. 9%- hypothyroid
5. 8%- tick borne disease: ie lyme, anaplasmosis

82% of dogs had a concurrent dz or serious condition. Not sure if any dogs had multiple conditions?

61% of dogs w/ DCM and/or CVD had concurrent medical conditions (Freeman, Rush et al, 2003)

RECENT REPORTS:

FDA release & Vet LIRN release June 27, 2019-

- Non DCM cardiac cases- "According to the medical records reviewed for the non-DCM cardiac disease cases, other cardiac changes were present on echocardiogram, including degenerative valvular disease, tricuspid and mitral valve regurgitation, and borderline to decreased left ventricular systolic function." Describes primary heart valvular problems that could be occurring in any dog. Is not specific to DCM.
- Taurine status- 38% of confirmed DCM dogs had low whole blood taurine.
- 40% of confirmed DCM dogs had normal whole blood taurine.
- 22% of confirmed DCM dogs had high whole blood taurine.
- Goldens were 37% of low taurine/confirmed DCM and 48% of all dogs w/ low taurine. Most over represented breed. Recent breed awareness of link to DCM to certain breeds?? (Kaplan, Stern et al 2018)
- FDA gives a few individual examples of how cases have progressed.
- "FDA encourages veterinary professionals to report well-documented cases of DCM in dogs whose illness is suspected of having ***a link to diet***."

RECENT REPORTS:

Diet-associated dilated cardiomyopathy in dogs: what do we know?- JAVMA Dec. 1, 2018 (Freeman, Stern et al)

- "The association between diet and DCM in dogs has generally not been much in the news since the early 2000s, but over the past few years, an increasing number of DCM cases involving dogs appear to have been related to diet"
- "…a true association has not been proven to exist."
- >240 dog survey international cardiologists- "possible diet-associated DCM represented 16% of all cases of DCM diagnosed by the respondents during this period." *Unpublished data (Fries)*
- "In 1995, veterinary cardiologists investigating the role of taurine deficiency in dogs with DCM suggested that certain breeds (eg, Golden Retrievers and American Cocker Spaniels) may be predisposed to taurine deficiency"
- "Later, certain types of diets, including lamb and rice, low-protein, and high-fiber diets were associated with taurine deficiency in some dogs." *studies cited from late '90's & early 2000's*
- "Subjectively, it also appeared that these dogs were frequently eating BEG diets containing foodstuffs such as kangaroo, duck, buffalo, salmon, lamb, bison, venison, lentils, peas, fava beans, tapioca, barley, or chickpeas as major ingredients "

SO WHAT IS GOING ON?

Likely multi-factorial:

- Individual nutritional deficiencies- approx. 70% of dogs in FDA report >50 lbs. 2018 APPA data- 33% of US dogs are >40 lbs.
- Reporting sampling bias- FDA and researchers asking for dogs w/ DCM eating "BEG" diets. This will skew population based results.
- Unknown actual total dog population incidence.
- Awareness- esp. among certain breed groups ie Goldens & Cockers.
- GF diets have been around for at least 20 years, why problem now?
- Is it related to a calorie and/or protein intake issue?
- Are our AAFCO protein and amino acid requirements okay for ALL dogs?
- It has been known for quite some time that certain ingredients can be linked to DCM. Why has there been no cause-effect further research into "new" pet food ingredients by the researchers until recently?
- What really does size of the pet food company/manufacturer have to do with

SUMMARY

- DCM is a complicated cardiac condition with many possible contributing factors
- We do not know the exact prevalence in overall dog population.
- Certain breeds are genetically predisposed to DCM.
- Links have been made to taurine & carnitine deficiencies & DCM in other breeds.
- Other nutritional factors may play a part ie vitamins/minerals, nutrient interactions
- Other serious medical conditions can complicate establishing cause of DCM.
- Recent FDA and research publications have both DCM dog case information and equal speculative statements that are presented to appear as facts which is confusing for Vets and pet parents.
- FDA has not recommended changing diets if dogs are eating a grain free diet.
- Much more clinical research needed to establish a true cause.

WHERE TO GO FROM HERE:

- More Meta-analysis and Retrospective Studies
- Prospective studies
- Feeding Trials for different foods

THANK YOU

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