High to Low Pulse Diet DCM CVCA FDA Prospective Case Series

Preliminary Data
Steven Rosenthal DVM, Diplomate ACVIM (Cardiology)
CVCA Cardiac Care for Pet
www.cvcavets.com

Outline

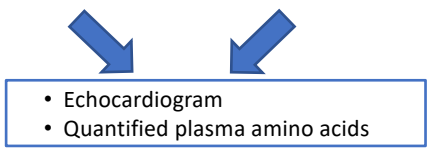
- Study design, Clinical Findings, and Recovery
  - 9 dogs with Dilated Cardiomyopathy (DCM)
  - Dechallenge high-pulse diets
- Plasma Amino Acid (AA) Concentrations
  - Elevated above controls at diagnosis
    - Decreased over time on low-pulse diets, taurine, and treatment
  - Contrast this trend with a 2020 challenge study
    - *Donadelli, et al.* measured baseline AA on a low-pulse diet
    - 15 AA increased after 6 months on high-pulse diets
- Potential Pathways Involved with DCM
- Future Research Areas

Study Design, Clinical Findings, and Recovery

9 Dogs with DCM: Study design

Time Point 0: Diagnosis
- Diagnosis with DCM
- Eating a high-pulse diet
- No Taurine supplement
- Diagnosed Aug through Dec 2018

Time Point 6: Recheck
- ~6 months later
- Eating a low-pulse diet
- Taurine supplement
  - +/- cardiac medication

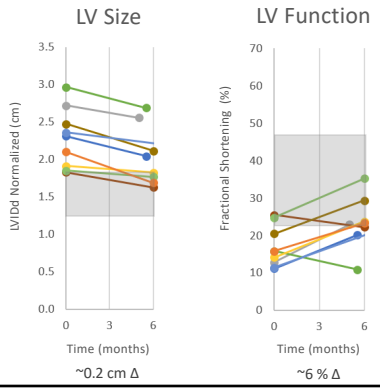


9 Dogs with DCM: Clinical Findings

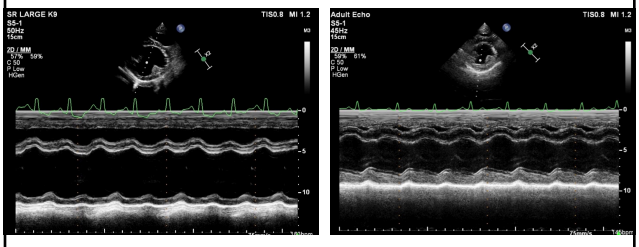
- Signalments
  - Median age: 6 years
  - 3 females, 6 males
  - Medium, large, and giant breeds
- 7 of 9 had Congestive Heart Failure (CHF)
- Whole Blood Taurine at Time Point 0
  - 1 dog: less than the reference range
  - Remainder were within or above the reference ranges

9 Dogs with DCM: Partial Recovery

DCM improved after changing to a low-pulse diet, starting taurine, +/- cardiac drugs.



Before and After Diet Change and Medication



Amino Acid Concentrations

Importance of Amino Acid Concentrations

- Venous amino acid concentrations*
  - Can be abnormal:
    - ↑ concentrations = ↑ organ metabolic turnover or catabolism
      - Humans with DCM have higher concentrations of some AAs
    - ↓ concentrations = ↓ organ metabolic turnover or anabolism
      - Humans with DCM have lower concentrations of some AAs
  - **CVCA Dechallenge Study:**
    - Time Point 0: ↑ concentrations (high-pulse diet)
    - Time Point 6: ≈ or ↓ concentrations (low-pulse diet, Tau, drugs)

Nutrients to organ

By-products of metabolism

Ivanisevic et al 2015

9 Dogs with DCM: Plasma Amino Acids

Time Point 0 (diagnosis)

- Essential
- Conditionally essential
- Nonessential
- Total

Blue: Greater than controls

*Controls: No history of DCM, ate low-pulse diets

9 Dogs with DCM: Plasma Amino Acids

Time Point 0 (diagnosis)

- Essential
- Conditionally essential
- Nonessential
- Total

Suggests:
↑ metabolic turnover

9 Dogs with DCM: Plasma Amino Acids

Time Point 0 (diagnosis)

- Essential
- Conditionally essential
- Nonessential
- Total

Blue: Greater than controls

Time Point 6 (months)

- Essential
- Conditionally essential
- Nonessential
- Total

Orange: Less than controls

*Controls: No history of DCM, ate low-pulse diets

9 Dogs with DCM: Plasma Amino Acids

Time Point 0 (diagnosis)
- Essential
- Conditionally essential
- Nonessential
- Total

Suggests:
↑ metabolic turnover

Time Point 6 (months)
- Essential
- Conditionally essential
- Nonessential
- Total

Suggests:
↓ metabolic turnover

Bottom Line: Decreasing Amino Acid Trend

9 Dogs with DCM: Plasma Amino Acids versus Controls

Amino Acid	Time 0
α-aminobutyric acid	↑
Aspartic acid	↑
Carnosine	↑
Cystine	↑
Glutamic acid	↑
Histidine	↑
3-methylhistidine	↑
Ornithine	↑
Serine	↑
Taurine	↑

Versus controls at Time Point 0:
- 57% greater than

Takeaway:
- ↑ metabolic turnover

↑ greater than, ≈ comparable, ↓ less than controls

9 Dogs with DCM: Plasma Amino Acids versus Controls

Amino Acid	Time 0	Time 6
α-aminobutyric acid	↑	≈
Aspartic acid	↑	↑
Carnosine	↑	≈
Cystine	↑	≈
Glutamic acid	↑	↑
Histidine	↑	↓
3-methylhistidine	↑	≈
Ornithine	↑	≈
Serine	↑	↓
Taurine	↑	↑

Versus controls at Time Point 6:
- 52% comparable
- 38% less than

Takeaways:
- ↓ trend
- ↓ metabolic turnover

↑ greater than, ≈ comparable, ↓ less than controls

Comparison to a Recent Challenge Study

*Donadelli RA, et al. A commercial grain-free diet does not decrease plasma amino acids and taurine status, but increased bile acid excretion when fed to Labrador Retrievers. *Trans Anim Sci* 2020;txaa141, https://doi.org/10.1093/tas/txaa141

Interstudy Comparison of Amino Acid Trends

- Focus on trends over time within each cohort/study
  - Increasing versus Decreasing
- Different study designs
  - Affect absolute values of amino acids, precludes comparison
- Challenge Study: *Donadelli, et al.* 2020
  - 15 plasma AAs ↑ after eating high-pulse diets for 6 months
- Dechallenge Study: CVCA study
  - 21 plasma AAs ↓ after eating low-pulse diets for 6 months and receiving taurine +/- cardiac drugs

Plasma Amino Acid	*Donadelli* 2020 6 months eating a high-pulse diet
Alanine	↑
α-aminobutyric acid	↑
Aspartic acid	↑
Glycine	↑
Histidine	↑
3-methylhistidine	↑
Leucine	↑
Lysine	↑
Methionine	↑
Ornithine	↑
Phenylalanine	↑
Hydroxyproline	↑
Taurine	↑
Tryptophan	↑
Tyrosine	↑

Suggests:
↑ metabolic turnover

Plasma Amino Acid	*Donadelli* 2020 6 months eating a high-pulse diet	CVCA Study ~1.5 years eating a high-pulse diet
Alanine	↑	↑
α-aminobutyric acid	↑	↑
Aspartic acid	↑	↑
Glycine	↑	≈
Histidine	↑	↑
3-methylhistidine	↑	↑
Leucine	↑	≈
Lysine	↑	↑
Methionine	↑	≈
Ornithine	↑	↑
Phenylalanine	↑	≈
Hydroxyproline	↑	≈
Taurine	↑	↑
Tryptophan	↑	≈
Tyrosine	↑	≈

In the CVCA study, half were greater than the controls after eating a high-pulse diet ~1.5 years and developing DCM.

Suggests:
↑ metabolic turnover

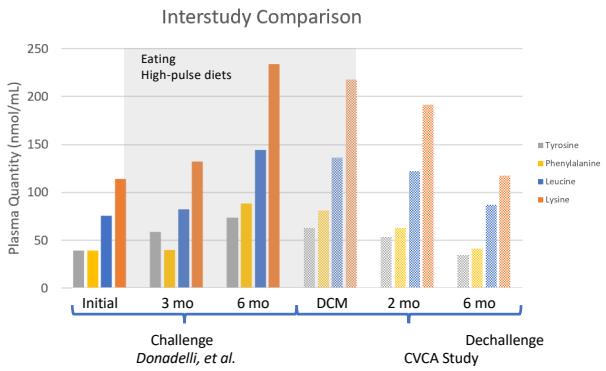
Plasma Amino Acid	*Donadelli* 2020 6 mo high-pulse Δ time	CVCA Study-Dogs with DCM ~1.5 yr high-pulse vs. controls	~6 mo eating a low-pulse diet vs. controls	~6 mo eating a low-pulse diet Δ time
Alanine	↑	↑	≈	↓
α-aminobutyric acid	↑	↑	≈	↓
Aspartic acid	↑	↑	↑	↓
Glycine	↑	≈	↓	↓
Histidine	↑	↑	↓	↓
3-methylhistidine	↑	↑	≈	≈
Leucine	↑	≈	↓	↓
Lysine	↑	↑	≈	↓
Methionine	↑	≈	≈	↓
Ornithine	↑	↑	≈	↓
Phenylalanine	↑	≈	↓	↓
Hydroxyproline	↑	≈	≈	≈
Taurine	↑	↑	↑	↑
Tryptophan	↑	≈	↓	≈
Tyrosine	↑	≈	↓	↓

Plasma Amino Acid	*Donadelli* 2020 6 mo high-pulse Δ time	CVCA Study ~6 mo low-pulse diet Δ time
Alanine	↑	↓
α-aminobutyric acid	↑	↓
Aspartic acid	↑	↓
Glycine	↑	↓
Histidine	↑	↓
3-methylhistidine	↑	≈
Leucine	↑	↓
Lysine	↑	↓
Methionine	↑	↓
Ornithine	↑	↓
Phenylalanine	↑	↓
Hydroxyproline	↑	≈
Taurine	↑	↑
Tryptophan	↑	≈
Tyrosine	↑	↓

Challenge study:
- 15 AAs ↑

Dechallenge study:
- 11 of 15 AAs ↓

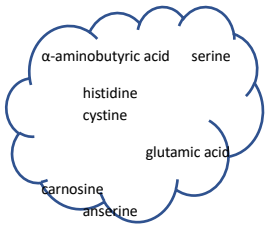
Interstudy Comparison



Potential Pathways Involved with DCM

Potential Pathways: Oxidative Stress

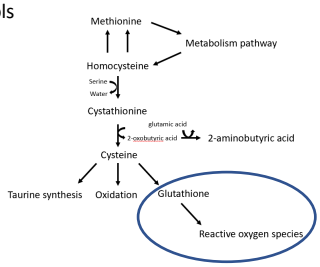
Time Point 0: Greater than controls



Potential Pathways: Oxidative Stress

Time Point 0: Greater than controls

α-aminobutyric acid serine histidine cystine glutamic acid carnosine anserine



Involved in myocardial glutathione synthesis to combat reactive oxygen species.

Potential Pathways: Oxidative Stress

Time Point 0: Greater than controls

α-aminobutyric acid serine histidine cystine glutamic acid carnosine anserine

Carnosine & Anserine are antioxidants made from Histidine.

In mice, anserine is cardioprotective versus doxorubicin-induced cardiomyopathy.

Act as antioxidants, suggesting a need

Potential Pathways: Altered Cardiac Energy Substrates

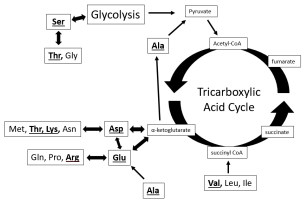
Time Point 0: Greater than controls

aspartic acid serine arginine lysine valine glutamic acid alanine

Potential Pathways: Altered Cardiac Energy Substrates

Time Point 0: Greater than controls

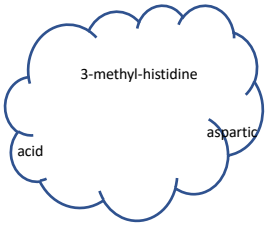
aspartic acid serine arginine lysine valine glutamic acid alanine



Precursors to the TCA cycle, creates ATP, used for energy during heart failure

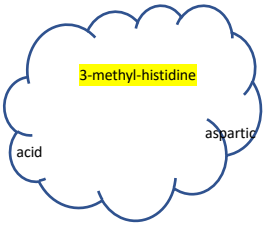
Potential Pathways: Structural Changes

Time Point 0: Greater than controls



Potential Pathways: Structural Changes

Time Point 0: Greater than controls

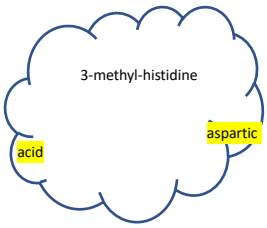


- Derivative of actin & myosin ≈ skeletal myofibrillar degradation
- ↑ in people with DCM
- People with DCM have ↑ cardiac myofibrillar gene expression

Suggests skeletal muscle breakdown for use by the heart

Potential Pathways: Structural Changes

Time Point 0: Greater than controls



- Dogs with severe DCM have left ventricular hypertrophy
- Aspartic acid accumulates in the cardiomyocytes of people during pressure-overload-induced hypertrophy

Potentially reflects left ventricular hypertrophy

Future Research Areas

Future Research Areas

- Evaluate additional plasma metabolites
  - Oxidative Damage
    - Glutathione and other antioxidants
    - Kynurenine, neopterin, Vitamin B
  - Cardiomyocyte Energy Substrates
    - Fatty acids
    - TCA cycle intermediates
  - Structural changes
    - BNP, troponin
    - Carnitine