High to Low Pulse Diet DCM
CVCA FDA Prospective Case Series
Preliminary Data
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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

- Echocardiogram
- Quantified plasma amino acids

9/7/20
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
  - \( \uparrow \) concentrations = \( \uparrow \) organ metabolic turnover or catabolism
  - Humans with DCM have higher concentrations of some AAs
  - CVCA Dechallenge Study:
    - Time Point 0: \( \uparrow \) concentrations (high-pulse diet)
    - Time Point 6: \( \approx \) or \( \downarrow \) concentrations (low-pulse diet, Tau, drugs)

- Profiling can be abnormal

Arterial blood
Venous blood
Metabolism

Nutrients to organ
products of metabolism

9 Dogs with DCM: Plasma Amino Acids

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

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

**Blue:** Greater than controls

**Orange:** Less than controls

*Suggests: \( \uparrow \) metabolic turnover

*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

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

Takeaway:
- ↑ metabolic turnover

↑ greater than, ≈ comparable, ↓ less than controls

Comparison to a Recent Challenge Study

9 Dogs with DCM: Plasma Amino Acids versus Controls

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Time 0</th>
<th>Time 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-aminobutyric</td>
<td>↑</td>
<td>≈</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Carnosine</td>
<td>↑</td>
<td>≈</td>
</tr>
<tr>
<td>Cystine</td>
<td>↑</td>
<td>≈</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Histidine</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>3-methylhistidine</td>
<td>↑</td>
<td>≈</td>
</tr>
<tr>
<td>Ornithine</td>
<td>↑</td>
<td>≈</td>
</tr>
<tr>
<td>Serine</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Taurine</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

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

Takeaways:
- ↓ trend
- ↓ metabolic turnover

↑ greater than, ≈ comparable, ↓ less than controls

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

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

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>6 mo High-pulse Δ time</th>
<th>6 mo Low-pulse Δ time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>↑</td>
<td>Δ</td>
</tr>
<tr>
<td>α-aminobutyric acid</td>
<td>↓</td>
<td>≈</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>↑</td>
<td>Δ</td>
</tr>
<tr>
<td>Cystine</td>
<td>↑</td>
<td>Δ</td>
</tr>
<tr>
<td>Histidine</td>
<td>↑</td>
<td>≈</td>
</tr>
<tr>
<td>L-α-amylotripeptide</td>
<td>↑</td>
<td>≈</td>
</tr>
<tr>
<td>Leucine</td>
<td>↑</td>
<td>Δ</td>
</tr>
<tr>
<td>Methionine</td>
<td>↑</td>
<td>Δ</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>↑</td>
<td>Δ</td>
</tr>
<tr>
<td>Proline</td>
<td>↑</td>
<td>≈</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>↑</td>
<td>≈</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>↑</td>
<td>Δ</td>
</tr>
<tr>
<td>Taurine</td>
<td>↑</td>
<td>≈</td>
</tr>
</tbody>
</table>

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

Involved in myocardial glutathione synthesis to combat reactive oxygen species.

Potential Pathways: Oxidative Stress

Time Point 0: Greater than controls

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
valine
alnine

Precursors to the TCA cycle, creates ATP, used for energy during heart failure
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
    • Xanthine, neopterin, Vitamin B
  • Cardiomyocyte Energy Substrates
    • Fatty acids
    • TCA cycle intermediates
  • Structural changes
    • BNP, troponin
    • Carnitine