EXERCISE-INDUCED COLLAPSE IN LABRADOR RETRIEVERS

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Exercise-induced collapse (EIC) in Labrador retrievers has received increased attention since 1999 because the incidence of this condition seems to be relatively high in competitive athletic retrievers. All colors (chocolate, black, and yellow) of retriever are affected, and the condition usually appears in highly enthusiastic dogs. EIC manifests as a progressive paraparesis eventually leading to complete collapse in some affected dogs; episodes are precipitated by vigorous activity. This condition may be noted as early as 6 months of age, when animals start training for field trials. Because dogs are at risk for experiencing additional episodes of collapse during strenuous training, a diagnosis of EIC can be career ending. Although this condition is usually not fatal, some animals die after a collapse episode. Therefore, it is essential that veterinary professionals, as well as pet owners and dog trainers, stop activity as soon as clinical signs are apparent.

The pathophysiologic mechanism(s) leading to EIC is not yet fully understood, but at least three universities are currently researching this condition. Although a wealth of data is not yet available, the findings in a few animals with suspected EIC may give clues as to the pathogenesis. Carnitine, an essential amino acid that plays a crucial role in energy production by controlling the influx of long-chain fatty acids into mitochondria, is decreased in the muscle and plasma in some dogs with EIC. The dogs with low carnitine concentrations were also found to have decreased pyruvate concentrations in the blood at various time points after vigorous activity. The changes in carnitine and pyruvate concentrations may be related to the cause of EIC or may be a result. It is still too early to confirm either.

For now, a diagnosis of EIC is confirmed by excluding all other conditions that can mimic clinical signs, including orthopedic disorders, various neurologic conditions, laryngeal paralysis, neuropathies, muscular dystrophies and other myopathies, congenital or acquired metabolic disorders, cardiovascular and respiratory disorders, anemia, and hypoglycemia.

Treatment for EIC is largely based on anecdotal experiences; however, even with treatment, it is likely that an affected dog will no longer be a competitive athlete. The disease does not appear to be progressive and in fact may improve as the animal ages. Most dogs with EIC can live long and happy lives as pets.
• Retrieving does precipitate an event.
• Occasionally, dogs collapse following extreme emotional excitement without overt physical activity.

**Physical Examination Findings**
- Animals with EIC are typically well muscled and fit.
- No specific physical examination findings have been clearly associated with EIC.
- Clinicians should make every effort to rule out other diseases that can mimic clinical signs.
- Dogs may exhibit the following clinical signs during or immediately after an EIC episode:
  - Weakness in all four limbs with lateral recumbency (common).
  - Paraparesis only, without complete collapse.
  - Cardiac and pulmonary auscultation within normal parameters.
  - Increased heart and respiratory rates (non-pathologic; reflects physical exertion).
  - Increased extensor tone in all four limbs.
  - Absent patellar (femoral nerve) reflex in dogs with collapse.
  - Elevated rectal temperature (>105°F).
  - No loss of consciousness, with the dog still exhibiting a desire to retrieve.
  - Absence of pain on palpation.

**Laboratory Findings**
- No specific laboratory findings have been clearly associated with EIC (all within normal parameters), and clinicians should make every effort to rule out other diseases that can cause a similar array of clinical signs.
- When evaluated immediately after or during an EIC episode, the following deviations (compared with resting samples) may be noted: $
  - Increased blood creatine kinase concentration.
  - Increased blood lactate concentration.
  - Increased blood pyruvate concentration (usually, but decreased concentrations have been seen in a small number of dogs with EIC).

**Blood lactate:pyruvate ratio** is normal in most dogs with EIC but can be increased in some dogs.

• Blood gas analysis:
  - Dramatically decreased arterial partial pressure of carbon dioxide ($\text{PaCO}_2$): 15–20 mm Hg.
  - Increased blood pH: 7.5–7.6.
  - Decreased bicarbonate ($\text{HCO}_3^-$). Interpretation: Metabolic acidosis (low bicarbonate); respiratory alkalemia (low carbon dioxide [$\text{CO}_2$]).

**Important Note:** These results are largely identical to those obtained from normal (unaffected breed-matched) animals after vigorous activity. The only difference may be that these changes occur more rapidly (within 5–10 minutes of mild to moderate exercise) in dogs with EIC.

• Carnitine concentration (total, free plasma, and free muscle) is decreased in some animals with EIC.

**Other Diagnostic Findings**
- No specific imaging or other common laboratory findings have been clearly associated with EIC (all within normal parameters).
- Clinicians should make every effort to rule out other diseases that can cause a similar array of clinical signs.

**Summary of Diagnostic Criteria**
First and foremost, clinicians must rule out other causes for collapse by performing the following procedures (remember, EIC is currently a diagnosis of exclusion).

**Routine Procedures**
• Complete physical and neurologic examination.
• Complete blood count.
• Serum biochemical analysis, including creatine Kinase to rule in or out other myopathies.
• Urinalysis.
• Chest radiography.
• Cardiac auscultation.
• Pulmonary auscultation.
• Electrocardiogram.
• Upper airway examination.

**Advanced Procedures**
• Free thyroxine concentration.
• Muscle biopsy.
• Pre- and postexercise lactate and pyruvate serum concentrations.
• Urinary organic acids.

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**CHECKPOINTS**
- Experts studying EIC have conflicting opinions regarding the significance of elevated body temperature. Some believe it is not related to the condition (citing references that confirm normal dogs have elevated body temperature when exercised). Others believe it is related to the underlying pathogenesis, saying that dogs affected by EIC develop temperature elevations much quicker than normal dogs.
Plasma, urine, and muscle carnitine concentrations.

Titer of antibodies directed against postsynaptic nicotinic acetylcholine receptors (myasthenia gravis test).

### Diagnostic Differentials

**Malignant Hyperthermia (Canine Stress Syndrome [CSS]):** Malignant hyperthermia is a relatively rare autosomal dominant condition that results from abnormal myofiber calcium homeostasis leading to prolonged muscular contraction, hyperthermia, and death (in some instances). The defect, at least in some dogs, has been linked to a mutated ryanodine receptor (RYR1 gene) on the sarcoplasmic reticulum. Dogs with CSS become progressively hyperthermic and have increased levels of lactate and CO$_2$ and increased extensor tone, which begin after exposure to inhalant anesthetics and/or depolarizing muscle relaxants. Occasionally, some dogs with CSS will have an episode in response to emotional or physical stress. The signs are very similar to those of EIC and consist of progressive ataxia after 5 to 15 minutes of moderate to vigorous exercise followed by hyperthermia, recumbency, and increased extensor tone with loss of the patellar reflex. No tests are currently available commercially to confirm a diagnosis of CSS, which must therefore be diagnosed by ruling out other causes for the clinical signs.

**Myasthenia Gravis:** Ruled out based on titer for anti-acetylcholine receptor (nicotinic) antibody. 

**Endocrinopathy:**
- Addison’s disease.
- Cushing’s disease.

**Hypothyroidism:** Ruled out based on free thyroxine concentration and level of thyroid-stimulating hormone. 

**Orthopedic Abnormality:** Ruled out through orthopedic examination, radiography, and/or joint fluid analysis.
- Degenerative joint disease.
- Cruciate ligament rupture.
- Bone fracture.
- Panosteitis.
- Hypertrophic osteodystrophy.
- Osteochondrosis desiccans.
- Fragmented coronoid process.
- Ununited anconeal process.
- Physisitis.
- Osteoarthritis.

**Spinal Cord Diseases:** Ruled out through neurologic examination, survey spinal radiography, cerebrospinal fluid analysis, spinal imaging procedures (myelogram, magnetic resonance imaging [MRI]), computed tomography [CT]), electrodiagnostic examination (electromyogram, nerve conduction velocity), and biopsy of nerve and/or muscle.
- Hansen type II intervertebral disk disease.
- Lumbosacral stenosis.
- Spinal fracture.
- Other spinal cord compressive disorders (neoplasia, abscess, granuloma).

**Polyneuropathy:** Ruled out through neurologic examination, electrodiagnostic evaluation (nerve conduction velocity, evoked potentials), and nerve biopsy.

**Cardiopulmonary (Perfusion) Abnormality:** Ruled out through auscultation, electrocardiography, and echocardiography.

**Hypoglycemia:** Ruled out through serum biochemical analysis; insulin:glucose ratio.

**Energy Deprivation (Congenital or Acquired Metabolic Disorder; Enzyme Deficiency):** Ruled out through urinary organic acid/amino acid/carbohydrate concentration.

**Laryngeal paralysis:** Ruled out through upper airway examination, electromyogram, or nerve conduction velocity.

**Myositis:** Ruled out through muscle biopsy and infectious disease titers.
- Infectious (Toxoplasma gondii, Neospora caninum).
- Inflammatory (idiopathic).
• Inherited/Degenerative Myopathy: Ruled out through muscle biopsy or biochemical analysis. $-$ $$
  — Duchenne muscular dystrophy (dystrophin deficiency).
  — Labrador retriever myopathy (type 2 fiber deficiency).

**TREATMENT RECOMMENDATIONS**

**Initial Treatment** $$
Because some dogs with EIC have low carnitine concentrations in the blood and muscle, empirical supplementation with the following medications may be indicated:
• L-Carnitine: 50 mg/kg PO bid.
• Coenzyme Q10: 100 mg PO sid.
• Riboflavin: 100 mg PO sid.

**Alternative/Optional Treatments/Therapy**

**7-Keto** $$
7-Keto is a breakdown product of dehydroepiandrosterone (DHEA). Some authors advocate its use, although the mechanism of action is unclear and there is no clear evidence to support its use. Dose: 100 mg PO bid.

**Phenobarbital:** $
• The reason(s) phenobarbital is effective in decreasing the number and severity of EIC episodes is unknown. However, in my opinion, this drug has proven most effective in treating EIC.
• Dose: 2–3.5 mg/kg PO bid.
• Standard therapeutic drug monitoring is required when phenobarbital is administered:
  — Serum concentration should be checked 2 weeks after starting phenobarbital or changing the dose to establish steady-state concentration.
  — Concentrations should be checked annually or twice annually thereafter.
  — Complete blood counts and serum biochemical analyses should be performed annually or twice annually.
  — Liver function should be monitored.
  — Once an animal has achieved steady-state concentration (approximately 2 weeks), phenobarbital must **never** be stopped abruptly because of the risk of seizures. To discontinue phenobarbital, the animal must be slowly weaned from the drug over 4 to 6 weeks or longer. Phenobarbital administration can be discontinued completely when the serum concentration is less than 10 µg/ml.

**Supportive Treatment in the Event of an Episode**
• The animal’s activity should be **stopped immediately**.
• If possible, the dog should be placed in a cool environment.
• Rectal temperature should be monitored:
  — If greater than 107°F, ice should be used to cool the dog (medial thighs, feet).
  — Cooling should be stopped when rectal temperature falls below 104°F and/or the dog is able to stand up.
• The dog should be monitored for signs of disseminated intravascular coagulation (spontaneous hemorrhage, prolonged clotting times).
• Seizures should be treated (e.g., phenobarbital, midazolam, diazepam).
• Signs often progress for 5 to 10 minutes after the first indication of collapse is noted.
• Affected dogs usually fully recover within 30 to 45 minutes.

**Patient Monitoring**
After collapse, it is important that the patient be monitored closely to determine the progression of the condition. Most animals will slowly recover from collapse within 30 to 45 minutes; however, a rare animal may continue to deteriorate and develop life-threatening perturbations. Patients should be monitored for:
• Signs of dyspnea. (Note: Excessive salivation that often occurs with collapse can sometimes negatively effect ventilation).
• Signs of disseminated intravascular coagulation: ecchymotic hemorrhages, petechiation, bleeding from orifices, prolonged clotting times, decreased platelets, and increased fibrinogen.
• Elevated temperature.

**Home Management**
• Most episodes of EIC can be prevented or minimized by decreasing the activity level in affected dogs.
• Activities associated with emotional excitement or anticipation should also be avoided.
• Most dogs with EIC will live a normal lifespan and function as happy pets.
**PROGNOSIS**

**Favorable Criteria**
- Mild, short-lived episodes.
- Dog does not completely collapse and shows minimal neurologic abnormalities (e.g., mild paraparesis, ataxia).
- EIC episodes elicited only with intense exercise.

**Unfavorable Criteria**
- Severe episodes (long duration, complete collapse).
- Episode easily elicited (e.g., mild exercise, emotional excitement).

**STANDARDS of CARE: EMERGENCY AND CRITICAL CARE MEDICINE**

- Most dogs (few exceptions) with EIC will not be able to compete in field trials.
- Breeding of affected animals (male or female) is not recommended pending further investigation into the inheritance of this disorder.

**Milestones/Recovery Timeframes**
Most animals will spontaneously recover within 30 to 45 minutes of collapse. The animal caretaker will usually be able to identify early signs of collapse (mild incoordination) as well as activities that typically result in collapse and be able to avoid or stop the activities before the animal collapses completely.

**Treatment Contraindications**
- Although EIC is not identical to CSS, the conditions may be difficult to distinguish clinically. Definitive confirmatory testing is not available for either disease. Genetic testing is available for CSS; however, it is possible (and likely) that more than one mutation could be causing CSS. Therefore, an animal may test negative for a genetic defect of the RYR1 gene yet still have the disease.
- It is good practice to avoid halothane anesthesia (and possibly other inhalant anesthetics) as well as depolarizing neuromuscular blocking agents in dogs suspected of having EIC. In conditions where avoidance of anesthetics is not possible, clinicians should pay careful attention to the rectal temperature and end-tidal CO2 of the dog while it is under anesthesia. Anesthesia should be stopped immediately if the temperature and CO2 levels rise precipitously and an underlying cause is not immediately identified.
- Specific treatment of fulminant CSS episode: Dantrolene (2–3 mg/kg IV or 3.5 mg/kg PO) should be given as soon as possible. 

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**RECOMMENDED READINGS**


