

# Exercise Induced Collapse in Labrador Retrievers: 2008

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## INTRODUCTION

Exercise induced collapse (EIC) is a common cause of episodic exercise intolerance and collapse in otherwise healthy, adult, Labrador Retrievers. Dog owners and professional trainers have recognized affected individuals for at least 20 years, but they have not had a name for the disorder. Veterinarians have speculated that the episodes might be due to heat intolerance, low blood sugar, electrolyte (sodium, potassium or chloride) disturbances, heart rhythm abnormalities, or an inherited muscle disorder. Dogs with EIC are normal at rest and able to tolerate mild to moderate exercise but occasionally become incoordinated and collapse after 5 to 15 minutes of strenuous exercise. It is common for related dogs (littermates) to be affected.

A comprehensive investigation into EIC has been ongoing for nearly a decade, involving investigators from the University of Saskatchewan (Sue Taylor, Cindy Shmon), the University of Minnesota (Ned Patterson, Jim Mickelson, Katie Minor) and the Comparative Neuromuscular Unit at the University of California (Diane Shelton). This article will describe the research and the results, and provide the reader with some insight into this syndrome.

## RESEARCH METHODS

- (1) Surveys were completed by owners of 225 Labrador Retrievers with EIC, and the results were analyzed.
- (2) Fourteen dogs with EIC were exercised according to a standardized strenuous exercise protocol during which they repeatedly retrieved a hand-thrown bumper for 10 minutes. Clinical parameters were measured and laboratory tests were performed before and after exercise and results were compared with 14 normal, exercise tolerant, Labrador Retrievers completing the same exercise protocol.
- (3) Pedigrees and whole blood were collected from dogs with EIC and their clinically unaffected (normal) relatives. Pedigree analysis was performed using software established for that purpose. DNA isolated from the blood of the affected and normal dogs was analyzed for similarities and differences and a whole genome scan was performed to determine the chromosome and then the particular site on the chromosome where linkage to EIC occurred. Once this was established, candidate genes in the region were sequenced in order to identify the actual genetic mutation causing EIC.

## RESULTS

### *Who gets EIC?*

EIC is the most common reason for exercise intolerance and collapse in apparently healthy Labrador Retrievers. Signs typically first become apparent in young dogs between 5 months and 5 years of age (average 12 months). Labradors of all colors (black, yellow, chocolate) are affected, and males and females are equally affected. Dogs with EIC are often described by their owners as being extremely fit and muscular with a very excitable temperament and lots of retrieving drive.

### *Description of Collapse*

Affected dogs can tolerate mild to moderate exercise, but occasionally, after 5 to 15 minutes of strenuous exercise, they develop weakness, apparent incoordination, and may collapse. Most owners report that during episodes of collapse their dog's rear legs are floppy and unable to support weight. It is common for the dogs to continue trying to run while dragging their rear legs. Although rear limb signs are most prominent, during some episodes of collapse dogs will be unable to rise and may actually lose the ability to voluntarily move any of their limbs. Staggering and falling to the side or difficulty maintaining balance is common during recovery from episodes. Most dogs with EIC are mentally normal, but some dogs (25%) have had one or more episodes during which the owners report that they seemed dazed or confused.

### *Trigger Activities*

Activities most often associated with inducing collapse episodes in EIC susceptible dogs include repetitive "fun" retrieves, land retrieves during training or at a field trial, excited play with other dogs and upland hunting for pheasant or other game. Collapse during swimming or during waterfowl hunting is less common.

### *Contributing Factors*

Owners were asked to speculate on factors that they felt contributed to causing collapse in their dogs. The most common factor implicated was excitement or stress associated with a trigger activity. Many owners reported that they "could tell" when their dog was at risk of having an episode because they were excessively excited even before they started the trigger activity. The use of live birds in training or trials, chasing crippled birds, and stress during training (difficulty finding a mark, electronic collar correction, repeating an unsuccessful retrieve) were all cited as factors that would sometimes lead to increased excitement or stress and promote collapse. A few severely affected dogs were reported to routinely collapse with very minimal exercise if they were in a highly excited state. In contrast, owners reported that their EIC affected dogs could engage indefinitely in moderately strenuous activity not associated with excitement such as jogging, hiking or running alongside a bicycle with no signs of collapse.

#### *Veterinary Evaluation of EIC Dogs*

Dogs with EIC are normal at rest. They are typically extremely fit and well muscled. Examinations of their heart and lungs are normal at rest and during collapse. After exercise, during collapse, EIC dogs have very high body temperatures (often > 108F, >42C), but this is not different from dogs without EIC exercised in the same manner, and the time that it takes them to cool down after exercise is not different. Dogs with EIC are not lame and they do not have sore joints, muscles, bones or spine before or after exercise. Nervous system examination is normal at rest, but patellar reflexes are diminished or absent in dogs with EIC during collapse and these do not reappear until after the dog has completely recovered, which usually takes 10 to 30 minutes. Routine blood analysis is normal at rest and there are only minor changes following exercise when compared with normal exercising Labradors. Dogs with EIC have normal thyroid gland function, and normal adrenal gland cortisol production. Muscle biopsies are normal. EIC is a distinct disorder that is different from heat stroke, malignant hyperthermia (MH), myasthenia gravis, mitochondrial myopathies and centronuclear myopathy (CNM).

#### *Long Term Outlook*

Dogs symptomatic for EIC must often be retired from the activities that cause them to collapse and if participation in these trigger activities is limited, these dogs can live normal lives. Dogs with EIC do not develop progressive systemic or nervous system dysfunction over time, and except for their EIC, they are normal. Many affected field trial dogs have been adopted out as pets, and if intense exercise, excitement and training stress are avoided, they typically never experience another episode of collapse.

Some dogs with EIC are able to continue to participate in trigger activities if the owner watches them carefully and halts exercise as soon as they notice subtle gait abnormalities. Their participation in prolonged strenuous exercise, especially if associated with a high state of excitement or stress or high environmental temperatures should be limited. Many dogs with EIC seem to be less prone to collapse as they age or after castration, perhaps because their activity and excitement levels decrease.

Dogs with EIC, even if they are older or neutered, must always be considered to be at risk for an episode of collapse, so they should be watched carefully. Owners and handlers of these dogs should make every effort to stop the dog's activity at the first hint of abnormality. Symptoms typically worsen for 3 to 5 minutes after exercise has been terminated, so dogs with EIC should be closely monitored after exercise, not just put away in the truck or kennel. A few affected dogs have died during exercise or (more commonly) while resting immediately after exercise - these dogs have not always been recognized as severely affected dogs, so all dogs with EIC should be considered at risk for a fatal episode.

#### *Treatment*

The best treatment in most dogs with EIC consists of avoiding intensive exercise in conjunction with extreme excitement and ending exercise at the first sign of weakness/wobbliness. There are, however, numerous anecdotal reports of dogs being able to resume trigger activities such as retriever training and competition when they are treated with the anti-seizure medication, Phenobarbital. Phenobarbital and other sedative drugs may simply decrease the dog's level of excitement or anxiety, thereby decreasing the likelihood of collapse. There are a few very successful field trial dogs on the circuit that have EIC and are only able to compete when they are receiving daily Phenobarbital. In some dogs, however, Phenobarbital administration will cause noticeably impaired judgment, interfering with training or trialing. Phenobarbital is a controlled drug with potential side effects, so it should only be administered under the direction and monitoring of a veterinarian.

#### *Heredity of EIC*

Pedigree analysis has established that the mode of inheritance for EIC is autosomal recessive, meaning that all dogs with EIC have received two mutant genes - one from each parent. This means that both parents of a dog with EIC are either carriers of EIC (1 mutant EIC gene) or affected by EIC (2 mutant EIC genes).

#### *The Mutation*

During the summer of 2007, the mutation causing EIC was identified and a reliable genetic (DNA based) test to look for this mutation was developed. Details regarding the mutation and the changes in nervous system function caused by the mutation cannot be released to the public until after scientific publication.

#### *Testing for EIC*

Testing will be performed at the University of Minnesota Veterinary Diagnostic Laboratory, and should be available by mid-summer, 2008. EDTA blood samples will be required, and must be submitted by a veterinarian who will verify identity (tattoo, microchip) for the dog being tested and will be able to help owners interpret their test results. Certification will be managed through the Orthopedic Foundation for Animals (OFA), similar to thyroid and hip screening. For more information about the test, billing, sample submissions and the process for EIC status certification see the University of Minnesota Veterinary Diagnostic Laboratory website:

<http://www.cvm.umn.edu/vdl/ourservices/canineneuromuscular/home.html>

The test will determine whether a dog is:

\*Affected by EIC (has 2 copies of the causative mutation: homozygous for EIC)

\*A carrier of EIC (has 1 copy of the causative mutation: heterozygous for EIC)

\*Clear of EIC (no copies of the causative mutation: normal)

#### UNDERSTANDING TEST RESULTS: THE INHERITANCE OF EIC

Every dog gets 2 copies of every gene - one from its dam and one from its sire. The mutation in the gene that causes EIC is inherited as an autosomal recessive trait, which means that all **affected dogs** (those showing signs of collapse) have 2 copies of the mutated gene - one that they got from their dam and one from their sire.

**Clear dogs are dogs that do not have any copies of the mutation.** These dogs do not have EIC and will not show signs of collapse. If bred, they will not pass a copy of the EIC mutation on to any of their puppies.

**Carriers, by definition, are dogs that have one copy of the mutated gene** that they got from either their dam or their sire and they have one normal copy of the gene that they got from the other parent. These dogs do not have EIC and will not show signs of collapse. They will, however, pass their copy of the mutated gene on to approximately half of their puppies.

**Affected dogs have 2 copies of the mutation**, one of which came from each parent. Dogs with 2 copies of the mutated gene (affected dogs) have EIC and most will show occasional signs of exercise intolerance or collapse when participating in trigger activities with a very high level of excitement or stress. Some affected dogs will never exhibit signs of EIC - this could be because they do not participate in high excitement strenuous activities or because they have a laid-back temperament.

#### WHAT TO DO IF YOUR DOG HAS EPISODES OF COLLAPSE

EIC is the most common cause of exercise intolerance and collapse in Labrador Retrievers that seem otherwise healthy, but it is important to realize that there are many other medical conditions that can cause similar signs. Complete veterinary evaluation should therefore be performed in any dog with exercise intolerance to eliminate treatable disorders such as low blood sugar, anemia, heart rhythm disturbances, laryngeal paralysis, joint or muscle disease, cauda equina syndrome, low blood cortisol, myasthenia gravis and epilepsy. If veterinary evaluation suggests that the dog may have EIC, your veterinarian should submit a blood sample to confirm the diagnosis.

If a collapsing Labrador Retriever is confirmed to have EIC (i.e. blood test confirms two copies of the EIC mutation), it should be recommended that participation in trigger activities be limited and that the dog be monitored closely so that exercise can be ended at the first sign of weakness/wobbliness. If the dog does collapse, (1) make sure that it has unobstructed breathing so it can hyperventilate to blow off heat, (2) offer water and ice orally, and (3) cool the dog by immersing it in cool water or wetting it down. Enforce rest until the dog is fully recovered.

If a collapsing Labrador Retriever does not have two copies of the EIC mutation, then the collapse must be due to something other than EIC. In my experience, the disorder most often confused with EIC is epilepsy, a condition that can be very difficult to diagnose in dogs. Labradors sometimes have a unique excitement-triggered form of epilepsy characterized by unusual episodic events (seizures) during which the dog maintains consciousness but experiences abnormalities of gait and/or balance that look a lot like EIC episodes. Clinically, the best differentiating feature between these epileptic seizures and EIC episodes seems to be that the epileptic seizures occur suddenly and resolve suddenly while dogs with EIC get gradually worse during a collapse episode and then gradually recover over 5 to 30 minutes. Later in life, many Labrador Retrievers with epilepsy also develop more typical generalized seizures, where they fall over, lose consciousness and paddle their legs.

#### BREEDING/TESTING RECOMMENDATIONS

From the limited testing that has been done so far, it appears that more than 25% of the Labrador Retrievers participating in field trials have at least one copy of the EIC mutation (i.e. they are either carriers or affected). The apparently very high frequency of the mutation causing EIC in the Labrador breed and the presence of the mutation in some of the most successful field trial lines make it unreasonable to suggest breeding only dogs that are clear of this mutation. There are many other factors to consider when breeding, including other health conditions and positive and negative inherited talents and traits. Breeders simply need to be selective in their breeding, avoiding the production of dogs that actually have EIC. All breeding dogs should be tested, and if carrier dogs are bred they should only be bred to dogs that are genetically clear of EIC so that affected puppies will not be produced (see Table). Puppy buyers can insist on documentation that the puppy they are buying does not have EIC. Ideally, whenever a dam or sire of a litter is a known carrier of EIC, each puppy should be tested before 7 weeks of age and if everything else is equal the pups that are clear of EIC are the ones that should go to homes interested in future breeding (see table). ■

##### TABLE

##### EIC: IMPLICATIONS FOR BREEDING

##### **Clear dogs: no copies of the mutation**

bred to a clear dog: 100% of pups clear

bred to a carrier: 50% of pups clear, 50% of pups carriers\*

bred to an affected: 100% of pups will be carriers

##### **Carrier dogs: one copy of the mutation**

bred to a clear dog: 50% of pups clear, 50% of pups carriers\*

bred to a carrier: 25% of pups clear, 50% of pups carriers, **25% of pups affected**

bred to an affected: 50% of pups carriers, **50% of pups affected**

##### **Affected dogs: two copies of the mutation** (breeding is not recommended)

bred to a clear dog: 100% of pups will be carriers

bred to a carrier: 50% of pups carriers, **50% of pups affected**

bred to an affected: **100% of pups affected**

\*puppies from carrier matings can be tested to determine which ones are clear and which ones are carriers

*I believe that it is important for me to disclose that, as one of the inventors, I will be sharing in royalties from this test. My recommendations for testing, however, arise from my honest belief that it is the right thing to do as a veterinarian and as a breeder, owner and lover of Labrador Retrievers.*

*This article will be published in both Retrievers ONLINE and the Retriever News so that it will be available to the widest range of retriever enthusiasts. I would like to take this opportunity to express my appreciation to all of the dog owners, breeders, veterinarians, trainers and trialers who have participated in this research during the last 10 years and, of course, to all the dogs.*

*Thank you,  
Sue Taylor*