

## **EXERCISE INDUCED COLLAPSE IN LABRADOR RETRIEVERS**

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A syndrome of exercise intolerance and collapse (EIC) has been recognized in young adult Labrador Retrievers.

Investigators from the University of Minnesota (EE Patterson, JR Mickelson, KM Minor), the University of Saskatchewan (SM Taylor, CL Shmon), and the Comparative Neuromuscular Unit at the University of California (GD Shelton) have been researching this condition for more than a decade

**This handout will summarize some of what we have learned about the syndrome of Exercise Induced Collapse in Labrador Retrievers.**

### ***WHO GETS IT?***

The syndrome of exercise intolerance and collapse (EIC) is a common inherited disorder in Labrador Retrievers. Black, yellow and chocolate Labradors of both sexes are affected, with the distribution of colors and sexes closely reflecting the typical distribution in field trials (black males most common). Signs first become apparent in young dogs - usually between 5 months and 3 years of age (average 14 months). In dogs used for field trials, this usually coincides with the age at which they enter heavy training. Littermates and other related dogs are commonly affected but depending on their temperament and lifestyle they may or may not manifest symptoms. Affected dogs exhibiting symptoms of collapse are usually described as being extremely fit, muscular, prime athletic specimens of their breed with an excitable temperament and lots of drive.

### ***HOW COMMON IS IT?:***

**EIC is the most common reason for exercise/excitement induced collapse in young, apparently healthy Labrador Retrievers.**

EIC is common in Labrador Retrievers, and now that we have identified the mutation we can test for the condition. Current data shows that 30% to 40% of Labradors are carriers (with one copy of the mutation) and 3% to 13% of dogs are affected (with 2 copies) and susceptible to collapse. The percentage of affected dogs varies with the populations of dogs being tested, and the reason for testing. The prevalence does not seem to be very different between field trial/hunt test dogs, show dogs and pet dogs. Most (>80%) affected Labradors (E/E: 2 copies of the mutation) experience at least one episode of collapse by the time they are 4 years of age. A few genetically affected (E/E) dogs never exhibit collapse, perhaps because they do not engage in the required strenuous activity with extreme excitement as required to produce collapse. DNA testing is the only way to know for certain whether a dog has EIC.

The research laboratory has tested 100-400 samples from each of the common retriever breeds - they have tested Golden Retrievers, Flat-Coated Retrievers, Chesapeake Bay Retrievers, Nova Scotia Duck Tolling Retrievers and Curly Coated Retrievers. They have also tested numerous dogs from many non-retriever breeds. So far, the mutation has only been found in Labrador retrievers, Curly coated retrievers, Chesapeake Bay Retrievers, Boykin Spaniels, German Wire-haired Pointers and Pembroke Welsh Corgi's.

### ***DESCRIPTION OF COLLAPSE***

Affected dogs can tolerate mild to moderate exercise, but 5 to 20 minutes of strenuous exercise with extreme excitement induces weakness and then collapse. Severely affected dogs may collapse whenever they are exercised to this extent - other dogs only exhibit collapse sporadically.

The first thing noted is usually a rocking or forced gait. The rear limbs then become weak and unable to support weight. Many affected dogs will continue to run while dragging their back legs. Some of the dogs appear to be incoordinated, especially in the rear limbs, with a wide-based, long, loose stride rather than the short, stiff strides typically associated with muscle weakness. In some dogs the rear limb collapse progresses to forelimb weakness and occasionally to a total inability to move. Muscles are relatively flaccid during collapse, although when restrained in lateral recumbency some dogs exhibit increased extensor tone in the forelimbs. Manipulation and palpation of the muscles, joints, and spine during or after an episode does not seem to cause discomfort.

Some dogs appear to have a loss of balance and may fall over, particularly as they recover from complete collapse. Most collapsed dogs are totally conscious and alert, still trying to run and retrieve during an episode but as many as 25% of affected dogs have had at least one episode where the owner reports that they appear stunned or disoriented during the episode.

It is common for the symptoms to worsen for 3 to 5 minutes even after exercise has been terminated.

**NOTE: A few affected dogs have died during exercise or while resting immediately after an episode of exercise-induced collapse so an affected dog's exercise should ALWAYS be stopped at the first hint of incoordination or wobbliness.**

### ***Veterinary Evaluation of Affected dogs***

Nervous system, cardiovascular and musculoskeletal examinations are unremarkable at rest in dogs with EIC as is routine blood analysis at rest and during an episode of collapse. These dogs do not experience heart rhythm abnormalities, low blood sugar, electrolyte disturbances or respiratory difficulty that could explain their collapse. Body temperature is remarkably elevated during collapse (average 107.1F [41.7C], many up to 108F [42.2C]), but this magnitude of body temperature elevation has been found in normal exercise-tolerant Labradors as well. Affected dogs hyperventilate and experience dramatic alterations in their blood carbon dioxide concentration (decreased) and their blood pH (increased) but these changes are also observed in the normal exercising dogs. Affected dogs always completely lose their patellar reflexes during collapse and for a short period of time during recovery - even while they are able to walk relatively normally. Testing for myasthenia gravis (ACh-R ABy) is negative. Thyroid gland function (T<sub>4</sub>, TSH) and adrenal gland cortisol production (ACTH Stimulation test) are normal. Affected dogs are negative for the genetic mutation known to cause malignant hyperthermia.

### ***Recovery from collapse***

Most dogs recover quickly but the recovery is gradual rather than instantaneous. Dogs are normal within 5 to 25 minutes with no residual weakness or stiffness. Dogs are not painful during the collapse or after recovery. Massage of the muscles or palpation of the joints or spine does not cause discomfort. Affected dogs are not stiff or sore or limping upon recovery.

### ***Body Temperature***

Body temperature is normal at rest in dogs with EIC but is almost always dramatically increased at the time of collapse (*temperature* >41.5 C, >107.6F). We have shown experimentally, however, that clinically normal Labrador Retrievers doing this type of exercise for 10 minutes routinely had similar dramatic elevations in body temperature yet exhibited no signs of weakness, collapse or disorientation. Dogs with EIC will pant hard during the time of collapse, in an attempt to cool off, but this is similar to normal dogs exercised in the same manner. The time it takes for dogs with EIC to return to their resting temperature after exercise is not different from normal Labrador Retrievers. Although temperature may play some role in EIC related collapse, and may even contribute to the death of some affected dogs, inability to properly regulate temperature is not the underlying problem in dogs with EIC.

## ***FACTORS CONTRIBUTING TO COLLAPSE IN DOGS WITH EIC***

**Ambient Temperature.** High ambient temperature does not seem to be necessary to induce collapse, but if the temperature is much warmer than what the dog is accustomed to, collapse may be more likely. Excessive panting (hyperventilation) in hot weather may be a contributing factor. Affected dogs are less likely to collapse in cold weather or while swimming, but some dogs have exhibited collapse while breaking ice retrieving waterfowl in frigid temperatures and some dogs have drowned when experiencing EIC -related collapse in the water.

**Excitement.** Dogs that exhibit the symptoms of EIC are most likely to have intense, excitable personalities, and it is very apparent that their level of excitement plays a role in inducing the collapse. There are some severely affected dogs who, if they are extremely excited, do not even require much exercise to induce the collapse. Dogs with EIC are most likely to collapse when engaging in activities that they find very exciting or stressful. This can include retrieving of live birds, participation in field trials, training drills with electric collar pressure and quartering for upland game.

**Type of Exercise.** Routine exercise like jogging, hiking, swimming, most waterfowl hunting and even agility or flyball training are not very likely to induce an episode in dogs with EIC. Activities with continuous intense exercise, particularly if accompanied by a high level of excitement or anxiety most commonly cause collapse. Activities commonly implicated include grouse or pheasant hunting, repetitive "happy retrieves", retrieving drills or repetition of difficult marks or blinds where the dog is being repeatedly corrected or is anticipating electric collar correction, and excitedly running alongside an ATV.

## ***DIAGNOSIS OF EIC***

Until October of 2008, EIC could only be diagnosed by systematically ruling out all other disorders causing exercise intolerance and collapse and by observing characteristic clinical features, history and laboratory test results in affected dogs. Even today, any Labrador Retriever with exercise intolerance should always have a complete veterinary evaluation to rule-out treatable conditions such as orthopedic disorders, heart failure, anemia, heart rhythm disturbances, respiratory problems, low blood sugar, cauda equina syndrome, myasthenia gravis, hypoadrenocorticism, and muscle disease. Genetic (DNA) testing for EIC can now be performed to confirm a suspected diagnosis of EIC.

## ***Inheritance***

EIC is a hereditary condition, with littermates and other related dogs commonly affected. It is inherited as an autosomal recessive trait. In 2007 the chromosomal locus (site) of the mutation causing EIC was found on chromosome 9, and the genetic mutation responsible for susceptibility to EIC was identified. This is a mutation in the gene for dynamin-1 (DNM1) that causes a change in the amount or function of the dynamin-1 protein in dogs homozygous for the mutation (E/E: affected). The scientific papers state that this mutation is "highly associated with EIC" - the wording required until experimental studies on the actual DNM1 protein function in the brain of dogs with EIC takes place.

Dynamin-1 is a protein expressed only in the brain and spinal cord where it plays a key role in repackaging synaptic vesicles containing neurotransmitters. DNM1 is not required during low level neurological stimulation, but when a heightened stimulus creates a heavy load on release of CNS neurotransmitters (as with intense exercise, a high level of excitement or perhaps increased body temperature) DNM1 is essential for sustained synaptic transmission in the brain and spinal cord. Dogs with 2 copies of the EIC mutation (E/E) are susceptible to collapse in those conditions.

**DNA testing for the genetic mutation causing EIC susceptibility can now be performed.** This is a reliable test for the actual mutation (not linkage) so results are definitive and accurate - determining with certainty whether a dog has one copy of the mutation (carrier), 2 copies of the mutation (affected) or no copies of the mutation (clear). Instructions for collecting and submitting samples for testing, sample shipping and the necessary forms are available on the website of the **Veterinary Diagnostic Laboratory at the University of Minnesota**. In addition to testing blood samples submitted by veterinarians from adult dogs or puppies, cheek swabs can now be submitted and litters of newborn puppies can be tested by sending in dewclaws. Frozen stored semen can also be tested from deceased sires.

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

**In Europe, the test is performed by Laboklin**

<http://www.laboklin.com>

### **LONG TERM OUTLOOK**

Dogs symptomatic for EIC are rarely able to continue training or competition. It seems that if affected dogs are removed from training and not exercised excessively the condition will not progress and they will be fine as pets. They are able to continue to live fairly normal lives if owners limit their intense exercise and excitement. Some dogs will seem to "get better" as they age and slow down their activity and their excitement level, but in others the tendency to collapse becomes stronger with age.

***It is important that owners of dogs with EIC be made aware that the dog's exercise should be stopped at the first hint of incoordination or wobbliness as some affected dogs have died during collapse when their owners allowed or encouraged continuing exercise.*** Not all of the EIC deaths have occurred in dogs rated as severely affected based on their number of episodes of collapse or the amount of activity required to induce an episode.

### **TREATMENT**

The best treatment in most dogs consists of avoiding known trigger activities and activities that involve intensive exercise in conjunction with extreme excitement especially in hot weather. Most dogs that are retired from training/competition or trigger activities like upland hunting live the remainder of their life without any episodes of collapse. Owners/trainers must always keep in mind the importance of ending exercise at the first sign of weakness/wobbliness if it does occur since these dogs are susceptible to collapse and death from EIC.

Medical treatment with the anti-convulsant Phenobarbital (2 mg/kg every 12 hours) has been effective at preventing or decreasing episodes in some dogs when restricting participation in trigger activities was not an option. In particular, some field trial dogs have been able to re-enter training and competition at a high level during treatment. The actual mechanism underlying the effectiveness of Phenobarbital in dogs with EIC is uncertain. It is possible that this drug just "takes the edge off" and decreases the dog's level of excitement, thus making it less likely that they will have an episode. This drug should only be administered with strict veterinary supervision and monitoring.

A few EIC affected male dogs have experienced improvement after neutering - with an improved ability to tolerate intensive exercise without collapse. Again, this improvement may be a result of a decrease in the general excitement level of the dog.

## UNDERSTANDING TEST RESULTS: THE INHERITANCE OF EIC

The test will determine whether a dog is:

Affected by EIC (has 2 copies of the causative mutation: E/E)

A carrier of EIC (has 1 copy of the causative mutation: E/N)

Clear of EIC (no copies of the causative mutation: N/N)

### EXPLANATION:

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.

**Carriers, by definition, are dogs that have one copy of the mutated gene (E/N)** 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 pass their copy of the mutated gene on to approximately half of their puppies.

- Carriers of EIC (E/N) are no more likely to experience exercise intolerance and collapse than Labradors who are clear of EIC. We believe that individual dogs that are carriers or clear who do experience episodes of collapse, exercise intolerance or disorientation have some other disorder and should receive full veterinary evaluation. Perhaps the most common disorder mistaken by owners and veterinarians for EIC is atypical epilepsy (see discussion in handout).

**Clear dogs are dogs that do not have any copies of the mutation. (N/N)**

- these dogs do not have EIC and will not show signs of collapse

**Affected dogs have 2 copies of the mutation (E/E)**

-both of their parents are either carriers or affected by EIC

-affected dogs have EIC and most will show signs of exercise intolerance or collapse when participating in trigger activities with a high level of excitement/stress

- a few genetically affected dogs (E/E) never exhibit any signs of EIC

- affected dogs will pass a copy of the mutation on to each of their offspring.

### IMPLICATIONS FOR BREEDING

**Carriers have one copy of the mutated gene and one copy of the normal gene. (E/N)**

They will pass their copy of the mutated gene on to approximately half of their puppies.

- if a carrier is bred to a non-carrier, none of their pups will be affected by EIC, but about half of their pups will be carriers.

- if a carrier is bred to another carrier, about 1/2 of their pups will be carriers, 1/4 of their pups will be non-carriers (clear) and 1/4 of their pups will be affected by EIC and susceptible to collapse.

- if a carrier is bred to an affected dog, about 1/2 of their pups will be carriers and 1/2 of their pups will be affected by EIC.

**So you can see, if you have a carrier dog or bitch, it is very important to know the EIC status of any dog you are breeding to.**

*NOTE: Entire litters can be tested (using dewclaws) to determine which pups are carriers and which are clear - allowing breeders to guarantee EIC status at the time the puppies are placed in new homes. These results will be 100% reliable but will not be eligible for verified permanent identification (VPI) registration with OFA. Blood samples or cheek swabs for VPI registration can be collected for testing from weaned older puppies (6-7 week old) if their microchip or tattoo is verified at the time of testing.*

## CERTIFICATION OF EIC STATUS

Testing for EIC is performed by the Veterinary Diagnostic Laboratory (VDL) at the University of Minnesota. Test results will be provided directly to the veterinarian submitting the sample and to the owner.

The VDL does not maintain a list that can be accessed by individuals interested in a particular dog's EIC status. The Orthopedic Foundation for Animals ([www.offa.org](http://www.offa.org)) does, however, host EIC data and provides OFA numbers for EIC clearances just like they do for hips, elbows and other heritable conditions. Results will only be listed on the OFA website if owners authorize the public release of their results. This list of EIC status for tested dogs can be accessed at <http://www.offa.org/search.html>. An individual dog's name or OFA certification number can be entered at the top of the page or the entire list of OFA certified tested dogs can be accessed by going halfway down the page to the second scrollable column of the section labeled "Report Type," scrolling down below the DNA subheading and clicking on Exercise Induced Collapse. Then click the "begin search" button at the bottom of the table and a list of all dogs with OFA certification (clear, carrier or affected) will be displayed alphabetically.

***Breeders are cautioned that simply reading on an advertisement or being told by a dog owner that a dog was tested EIC clear is not necessarily reliable information. Owners of potential breeding dogs should be encouraged to obtain OFA certification to document their test results and make them available to the public.***

## VETERINARY REFERENCES

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***DISCLOSURE:*** Dr. Taylor is a patent owner of the genetic test for EIC and receives a portion of the proceeds from this test.

***TESTING:*** Sample collection for EIC testing is available at the WCVI Small Animal Clinic (306-966-7126).

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