A syndrome of exercise intolerance and collapse (EIC) has been recognized in otherwise normal Labrador Retrievers. Investigators from the University of Minnesota (Ned Patterson, Jim Mickelson, Katie Minor), the University of Saskatchewan (Sue Taylor, Cindy Shmon), and the Comparative Neuromuscular Unit at the University of California (Diane Shelton) have been researching this condition for more than 15 years.

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

WHICH LABRADORS GET 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. Signs often first become apparent in affected dogs when they are young - 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 are otherwise normal and are often 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 Labrador retrievers that seem otherwise normal and healthy.

EIC is common in Labrador Retrievers, and now that we have identified the causative mutation we can test for the condition. Current data from the first 10,000 Labradors tested shows that 30% to 40% of all Labradors tested have been carriers (with one copy of the mutation: E/N) and 3% to 14% of dogs have been affected (with 2 copies: E/E) and susceptible to collapse. This wide variability in proportion of affected dogs results from evaluation of samples from different populations of dogs (samples submitted from dogs competing in shows and trials versus samples submitted by veterinarians from non-collapsing dogs being tested pre-breeding and collapsing dogs being tested searching for a diagnosis). Interestingly, the prevalence of carriers is not different between field trial/hunt test dogs and show dogs from any of these sampling populations.

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. Most competitive dogs are unable to continue training and competing at a high level but if trigger activities can be avoided, dogs with EIC live normal lives. A few genetically affected (E/E) dogs never do exhibit collapse, perhaps because they do not engage in the required strenuous activity with extreme excitement that is required to produce collapse. DNA testing is the only way to know for certain whether a dog has EIC.
OTHER BREEDS

The research laboratory at the University of Minnesota has tested 100-300 samples from many of the other 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 normal and collapsing dogs from many other other working and sporting breeds including American Water Spaniels, Newfoundlands, Portuguese Water Dogs and Border Collies. So far, the mutation has only been found in Labradors, Curly coated retrievers, Chesapeake Bay Retrievers, German Wirehaired Pointers, Cocker Spaniels, Boykin Spaniels, Bouvier des Flanders, Old English Sheepdogs and Pembroke Welsh Corgis.

DESCRIPTION OF COLLAPSE

Dogs with EIC 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 and dogs may 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 of the rear limbs are relatively flaccid during collapse, and there is loss of the patellar reflex during an episode and for a short period during recovery. 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.

Dogs worsen after exercise. It is common for the symptoms to worsen for 3 to 5 minutes even after exercise has been terminated. A few affected dogs have died during exercise or while resting immediately after an episode of exercise-induced collapse. An affected dog's exercise should ALWAYS be stopped immediately 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 is common in normal exercise-tolerant Labradors without EIC as well. Dogs affected by EIC hyperventilate and experience dramatic alterations in their blood carbon dioxide concentration (decreased) and their blood pH (increased) but these changes are also observed in normal exercising dogs as they pant to blow off heat. Testing for myasthenia gravis is negative as is testing for hypothyroidism, hypoadrenocorticism (low cortisol) and 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. 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.
FACTORS CONTRIBUTING TO COLLAPSE ON A GIVEN DAY

Ambient Temperature. Hot weather is not necessary to induce EIC-related collapse, but if the temperature is very warm, collapse is more likely. Affected dogs are less likely to collapse in cold weather or while swimming, but dogs have exhibited collapse while breaking ice retrieving waterfowl in frigid temperatures and 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. Dogs with EIC are most likely to collapse when engaging in activities that they find very exciting or stressful. This can include retrieving or chasing live birds, participation in field trials, training drills with electric collar pressure and quartering for upland game.

Type of Exercise. Routine exercise like jogging or hiking is 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 pheasant hunting, repetitive "happy retrieves", repetition of difficult retrieves especially where the dog is having trouble finding a bird or is receiving or anticipating electric collar correction, and excitedly running alongside an all terrain vehicle.

Body Temperature. Body temperature is normal at rest in dogs with EIC and is dramatically increased during collapse (often >41.5 C, >107.6F). Temperatures are not different from those seen in unaffected Labrador Retrievers doing the same type and amount of exercise. Dogs lose body heat through panting, so all dogs with these dramatic elevations in body temperature will pant hard in an attempt to cool off. Although the elevated temperature after exercise may play a role in EIC related collapse (making dogs more dependent on dynamin1 function – see below), 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.

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, low blood cortisol, cauda equina syndrome, myasthenia gravis, and muscle disease. Genetic (DNA) testing can now be easily performed to confirm a suspected diagnosis of EIC. Because there are so many potential causes of exercise intolerance in dogs, there has been a recent tendency to call the EIC syndrome caused by homozygosity for the dynamin-1 mutation dynamin-associated EIC (d-EIC).

Inheritance

EIC is a hereditary condition, with littermates and other related dogs commonly affected. EIC is inherited as an autosomal recessive trait which means that both the sire and the dam must be at least carriers (E/N) for one of their offspring to be affected. In 2007 the chromosomal locus (site) of the mutation causing EIC was found, 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 that have two copies of the mutation (homozygous: E/E: affected). The scientific papers state that this mutation is "highly associated with EIC" – this is the wording required until experimental studies on the actual amount and function of DNM1 protein in the brains of dogs with EIC can be completed.
Mechanism of Collapse

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

Testing

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 (E/N: carrier), 2 copies of the mutation (E/E: affected) or no copies of the mutation (N/N: 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, cheek swabs can be submitted by veterinarians from adult dogs or weaned puppies, 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

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.

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 historical number of episodes of collapse or the amount of activity required to induce previous episodes of collapse.

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 exhibiting any further 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 EIC episodes in some affected 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 Phenobarbital 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 an improved ability to tolerate intensive exercise without collapse after neutering. 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

Validated testing for EIC is available through the Veterinary Diagnostic Laboratory at the University of Minnesota in North America. Further information regarding EIC and EIC testing can be found on the University of Minnesota VDL website:

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

The test will determine whether a dog is:
Clear of EIC (no copies of the causative mutation: N/N)
A carrier of EIC (has 1 copy of the causative mutation: E/N)
Affected by EIC (has 2 copies of the causative mutation: E/E)

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.

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 EIC-related collapse

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 EIC-related collapse. They will pass their copy of the mutated gene on to approximately half of their puppies.

Affected dogs have 2 copies of the mutation (E/E)
Both of their parents are either carriers (E/N) or affected by (E/E) 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 (>80% collapse before 3 years of age)
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 a copy of the mutated gene on to approximately half of their puppies.

- if a carrier is bred to a clear dog, 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.*

**TESTING LITTERS**

When the dam or sire of a litter is a carrier of EIC, it is desirable to test the litter at birth to learn the EIC genetic status of each puppy. This knowledge may determine which puppies go to which homes. Entire litters can be tested using dewclaws snipped off and placed in individual tubes. Care should be taken to not cross-contaminate dewclaws from one pup with blood from another pup during dewclaw collection. The results from dewclaw DNA testing 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. The fee charged by the laboratory is $65.00. Cheek swabs are the most economical way to test adult dogs and weaned puppies as they can be sent through the regular mail with no special handling. Test results will be provided directly to the veterinarian submitting the sample and also to the owner.

The VDL does not maintain a list that can be accessed by individuals interested in a dog's EIC status.

The Orthopedic Foundation for Animals (www.offa.org) does, however, host EIC data and provides OFA numbers for EIC clearances just like they do for hips, elbows, eyes, centronuclear myopathy (CNM) results and other heritable conditions. Results will only be listed on the OFA website if owners authorize the public release of their results. Owners must FAX or mail their EIC test result form (obtained from the VDL) to the OFA to have their result posted. The fee is $15 for individual dogs or $30 for a litter – there is no charge for posting results from affected dogs.

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 website (other than OFA) 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 others who might be interested in breeding to their*
dogs one day. If a dog does not have their EIC result listed on OFA you should ask the owner to provide you with a copy of the laboratory result they obtained.

COLLAPSING LABRADOR THAT DO NOT HAVE EIC

Occasionally we hear about dogs experiencing recurrent episodes of incoordination or collapse with exercise that are not EIC affected – they are either EIC carriers (E/N) or EIC clear (N/N). In many cases there are abnormal physical findings detected at rest (heart murmurs, muscle atrophy, pain, etc) helping to distinguish these dogs from dogs with EIC-related collapse. In others the collapse episodes are subtly different from EIC-related collapse. For example, the age of onset may be older, the episodes may be more sudden in onset (less progressive as exercise continues), the episodes may involve all 4 legs at once (instead of rear legs first), muscle tone may be increased (instead of decreased), mentation may be abnormal (instead of normal) or affected dogs may seem painful during an episode (unlike EIC). The episodes of exercise intolerance in these dogs can be attributed to a number of different disorders including joint pain, heart failure, anemia, heart rhythm disturbances, laryngeal paralysis, lung disease, low blood sugar, low blood cortisol, cauda equina syndrome, myasthenia gravis, and muscle disease. It appears that one of the most common disorders causing episodes of exercise intolerance or collapse after exercise that can be confused with EIC in Labrador retrievers is an atypical seizure disorder.

Atypical Seizures / Paroxysmal Dyskinesia. An episodic movement disorder that may be a form of focal motor seizure has been commonly recognized in Labrador Retrievers. This disorder has been called atypical epilepsy, paroxysmal dyskinesia or episodic dyskinesia. Most Labrador retrievers presenting with these episodes have idiopathic epilepsy. The episodes in some dogs are most likely to occur upon waking or being startled, but in many dogs episodes seem to be triggered by exercise, excitement or hyperventilation, leading to confusion with EIC. Signs are different, however, from typical EIC episodes. Some dogs simply stagger and look dazed or confused for a few seconds or minutes and then recover, without ever falling over. Others have a 2 to 5 minute episode (occasionally longer) where they appear anxious and are unable to stand erect and walk but are able to crawl to their desired location. Some dogs seem to have a severe loss of balance during episodes. Affected dogs maintain consciousness and can obey commands during episodes. Some dogs have a dramatic decrease in their episode frequency when treated with chronic oral anticonvulsant therapy and some affected dogs develop more classical generalized tonic-clonic (loss of consciousness, falling to their side, paddling) seizures later in life.

Heat exhaustion / Heat stroke. Before we were able to test for and diagnose EIC, there were many who felt that EIC collapse episodes were simply a manifestation of recurrent heat exhaustion or heat stroke. The collapse episodes we see in dogs with EIC are, however, very different from collapse episodes associated with heat stroke. Heat stroke severe enough to cause collapse in a dog is life-threatening. Recovery, if it does occur, is slow and prolonged (hours to days) even with intensive treatment. Many affected dogs progress to kidney failure and death. Laboratory evaluation reveals a dramatic increase in the muscle enzyme CK. Mentation changes that are severe, progressive and persistent (for hours to days) occur in 80% of dogs collapsed due to heat stroke. Significant blood vessel wall injury leads to blood clots forming within blood vessels, disseminated intravascular coagulation (DIC), low blood platelets and damage to multiple organs. In contrast, dogs with EIC-related collapse show no laboratory abnormalities and they recover quickly - happy and running around within 5 to 25 minutes. Besides the severity of collapse episodes, the recurrent nature of EIC-related collapse and the fact that collapse can occur even on days with moderate or cool ambient temperatures helps to distinguish EIC from heat-related illness.
VETERINARY REFERENCES


Minor KM, Patterson E, Gross SD, Keating MK, Taylor SM, Johnson GS, Todd-Thomas K, Ekenstedt KJ, Mickelson JM. Frequency of the canine exercise induced collapse(EIC) gene in diverse breeds. presented as a poster (Patterson) and published in the Proceedings of the Scientific Forum of the American College of Veterinary Internal Medicine, June 2009, Montreal.


DISCLOSURE: Dr. Taylor is a patent owner of the genetic test for EIC and receives a portion of the proceeds from each EIC test performed by the University of Minnesota Veterinary Diagnostic laboratory.

Updated January 2014
IMPORTANT EIC FACTS

1. EIC is the most common reason for exercise and excitement induced collapse or wobbly gait in Labrador retrievers that seem otherwise normal and healthy.

2. Most dogs with EIC exhibit a characteristic pattern of collapse starting with rear limb weakness. They may continue to walk or run while dragging their back legs. EIC collapse progressively worsens as the dog continues to exercise and may even continue to worsen for a few minutes after exercise is halted.

3. All exercising Labrador retrievers will have high body temperatures after strenuous activity. It is not unusual for both EIC affected dogs and EIC unaffected dogs to have temperatures greater than 107°F (41.7°C) after 10 minutes of retrieving.

3. EIC-related collapse is not painful and typically resolves after 5-25 minutes of rest.

4. A severe episode of EIC collapse can be fatal.

5. Most (>80%) dogs that have EIC are observed to collapse at least once before the age of 3 years. A few genetically affected dogs never collapse – probably because they never experience the right mix of exercise and excitement.

6. Activities involving continuous intense exercise with excitement or stress are most likely to trigger episodes of EIC-related collapse.

6. The only way to know for certain whether or not a dog has EIC is through DNA testing.

7. A mutation in the gene for dynamin-1 (DNM1) causes susceptibility to EIC. EIC is an autosomal recessive inherited trait, meaning that to be affected (and susceptible to collapse) a dog must have two copies of the mutant gene – one inherited from each parent.

8. DNA testing for the DNM1 mutation is available through the Veterinary Diagnostic Laboratory (VDL) at the University of Minnesota. Testing can be performed on cheek swabs, blood, or puppy dewclaws. Results will determine whether a dog has EIC (2 copies of the mutation: E/E), is a carrier of EIC (1 copy of the mutation: E/N), or is clear of the mutation (N/N).

9. Results from EIC testing performed at the VDL can easily be posted on the Orthopedic Foundation for Animals website (www.offa.org) along with hip, elbow, eye and CNM certifications, making the results available to breeders evaluating the suitability of listed dogs for breeding purposes.

10. Unfortunately many owners have not yet posted their dog’s EIC test results on the OFA website, making it impossible for interested parties to verify the test results. If owners wish to have their result listed they simply need to send the VDL test result plus a nominal fee to the OFA.