

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.

A comprehensive study of this condition is underway involving collaborators from the Western College of Veterinary Medicine (WCVN) of the University of Saskatchewan (Taylor, Shmon), the College of Veterinary Medicine at the University of Minnesota (Mickelson, Patterson, Minor), and the Comparative Neuromuscular Unit at the University of California (Shelton). The objectives of this study are to (1) describe the syndrome so that it can be recognized by dog owners, veterinarians and trainers, (2) to thoroughly evaluate affected dogs to try to establish an efficient means of diagnosis and to gain some insight into the cause of the collapse and (3) to determine the genetic basis for the collapse syndrome. This research has been supported by generous grants from the Morris Animal Foundation and the WCVN's Companion Animal Health Fund.

This document will summarize some of what we have learned in the last 7 years about the syndrome of Exercise Induced Collapse in Labrador Retrievers. Descriptions of the syndrome and the results of our experimental study have been submitted for publication in the veterinary literature.

WHO GETS IT?

The syndrome of exercise intolerance and collapse (EIC) is being observed with increasing frequency in young adult Labrador Retrievers. Most, but not all, affected dogs have been from field-trial breedings. 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.

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. All of the factors important in inducing an episode have not yet been well established.

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. 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 but as many as 25% of affected dogs will 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.

Most dogs recover quickly and 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. (*AJVR 60(1):88-92, 1999*). 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, and may even contribute to the death of some affected dogs, inability to properly regulate temperature does not appear to be the underlying problem in dogs with EIC.

FACTORS CONTRIBUTING TO COLLAPSE IN DOGS WITH EIC

Ambient Temperature. Actual ambient temperature does not seem to be a critical factor contributing to collapse, but if the temperature is much warmer or the humidity is much higher than what the dog is accustomed to, collapse may be more likely. Affected dogs are less likely to collapse while swimming than when being exercised on land. There are severely affected dogs, however, who 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 running alongside an ATV.

VETERINARY EVALUATION OF AFFECTED DOGS / MAKING A DIAGNOSIS

Nervous system, cardiovascular and musculoskeletal examinations are unremarkable 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. Testing for myasthenia gravis (ACh-R ABx) is negative.

Thyroid gland function (T₄, TSH) and adrenal gland cortisol production (ACTH Stimulation test) appear to be normal. Brainstem, auditory evoked response (BAER) testing of a few affected dogs at rest and during an episode of collapse were normal. Affected dogs are negative for the genetic mutation known to cause malignant hyperthermia in dogs (mutation of the skeletal muscle ryanodine receptor RyR1).

EIC is the most common reason for exercise/excitement induced collapse in young, apparently healthy Labrador Retrievers. Until recently, 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. Any Labrador Retriever with exercise intolerance should always have a complete veterinary evaluation to rule-out treatable conditions causing or contributing to their collapse such as orthopedic disorders, heart failure, anemia, heart rhythm disturbances, respiratory problems, low blood sugar, cauda equina syndrome, myasthenia gravis, hypoadrenocorticism, and muscle disease prior to testing for EIC.

LONG TERM OUTLOOK

Symptomatic dogs 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 pretty normal lives if owners limit their intense exercise and excitement. Many dogs will seem to "get better" as they age and slow down their activity and their excitement level. ***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 intensive exercise in conjunction with extreme excitement and ending exercise at the first sign of weakness/wobbliness. A few dogs have, however, responded to medical treatment to the degree that they can re-enter training and competition at a high level. Each of the treatments listed below has been effective in a few dogs, but none of them has been 100% effective in all dogs.

Treatment as a metabolic myopathy. We initially felt that EIC was a metabolic myopathy caused by an enzyme deficiency leading to a defect in oxidative metabolism within the brain and muscle. Carnitine is a compound normally found in high concentrations in muscle and brain that is necessary for transport of fatty acids into the mitochondria for energy production in these tissues and approximately 30% of dogs with EIC have lower than normal levels of muscle carnitine. A few affected dogs may have had a positive clinical response to oral supplementation with carnitine (50mg/kg 2X/day), CoEnzyme Q10 (100mg/day) and Riboflavin (100 mg/day) - a standard cocktail for metabolic myopathies/neuropathies.

Treatment with 7-KETO. There is anecdotal evidence that a few severely affected dogs have responded positively to a nutraceutical called 7-KETO. This is a breakdown product of the hormone dehydroepiandrosterone (DHEA), a steroid made by the adrenal glands and brain. The dosage used has been 100 mg twice each day. The precise mechanism of action of 7-KETO in affected dogs is unknown, but it has demonstrated positive effects on energy production in the muscle and brain as well as acting as a neuroactive steroid, with effects on several neurotransmitter receptors in the brain.

Treatment with Phenobarbital. There are now numerous reports of severely affected dogs improving when they were treated with Phenobarbital (2 mg/kg every 12 hours or every 24 hours). The actual mechanism underlying its effectiveness in dogs with EIC is uncertain. Some dogs have shown a positive response with serum drug concentrations far below what is considered therapeutic for anticonvulsant activity. 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.

DIFFERENTIATING EIC FROM HEAT STROKE

There have been a number of good veterinary reviews of heat stroke in dogs recently and the syndrome we are seeing with EIC is very different. With heat stroke - induced collapse in dogs you expect to see a very slow or prolonged recovery that can take hours to days, or else progression to death. Laboratory evaluation reveals a dramatic increase in CK (usually 7-11X normal). Mentation changes that are severe, progressive and persistent (for hours to days) occur in 80% of affected dogs and significant endothelial injury leads to microvascular thrombosis, DIC, thrombocytopenia and bleeding as well as acute renal failure in most patients. In contrast, dogs with EIC collapse without showing laboratory abnormalities and they recover quickly - happy and running around within 5 to 25 minutes.

DIFFERENTIATING EIC FROM MALIGNANT HYPERTHERMIA

We have also learned enough about EIC to say with certainty that it is not the same as malignant hyperthermia (MH). The Minnesota collaborators in the EIC Project (Mickelson et al) recently confirmed that in dogs as in other species MH it is caused by a mutation in the calcium release channel of the sarcoplasmic reticulum in skeletal muscle – the ryanodine receptor. All of the affected EIC dogs evaluated at the WCVM were genotyped and tested for the known ryanodine receptor mutation and for linkage to other sites on chromosome 1, eliminating this mutated gene as the cause of EIC. Dogs with collapse due to MH typically look very different from our dogs with EIC. Their muscles are rigid (not flaccid like EIC) and they have increased CK in their serum. Histologically their muscles show rhabdomyolysis (our dogs muscles are normal). Dogs with MH often hypoventilate due to persistent muscular contraction so they are hypercarbic (where dogs with EIC hyperventilate).

DIFFERENTIATING EIC FROM A MITOCHONDRIAL MYOPATHY

Although our initial study of dogs with EIC was designed to detect a mitochondrial myopathy (a defect in the oxidative metabolism leading to energy production in muscle), the EIC syndrome as we know it does not have many of the classical features of a mitochondrial myopathy. Most dogs with mitochondrial myopathies have severe exercise intolerance that can be consistently demonstrated with even mild exercise. Most develop extreme lactic acidemia with even mild exercise and an elevated lactate to pyruvate ratio. Many have “ragged red fibers” demonstrated on histopathology which are really just subsarcolemmal mitochondria as well as ultrastructural changes to the mitochondria - none of this is evident in dogs with EIC and it has become apparent that dogs with EIC suffer more from neurologic dysfunction than from muscular weakness.

HEREDITY

Littermates and other related dogs are commonly affected, as expected with a hereditary condition. Clinically unaffected dams and sires commonly produce litters with more than one affected dog and pedigree analysis strongly supports an autosomal recessive mode of inheritance.

DNA harvested from the blood of affected dogs and their relatives has been used to perform a full genome scan at the University of Minnesota in order to identify a genetic marker for EIC, and find the genetic mutation causing EIC. This has been a slow and tedious process but significant progress has been made in 2007. The chromosomal locus (site) of the mutation was found, and recently the probable causative mutation responsible for susceptibility to EIC has been identified.

Researchers at the University of Minnesota (Patterson, Mickelson and Minor) have developed a genetic (DNA based) test to look for the probable causative mutation leading to EIC and are able to perform that test on a research basis. This test has not yet been verified through functional studies, or peer reviewed, but they are confident in the test's ability to provide a very high likelihood of genetic status for EIC (*affected, carrier or clear*). Participation in the testing and test results are strictly confidential and will only be disclosed to the owner of the tested dog.

UNDERSTANDING TEST RESULTS: THE INHERITANCE OF EIC

In exchange for allowing them to sample your dog to advance the research into how common the mutation is in the Labrador population, the laboratory in Minnesota will provide you with test results, letting you know whether your dog is:

Affected by EIC (*has 2 copies of the probable causative mutation*)

A carrier of EIC (*has 1 copy of the probable causative mutation*)

Clear of EIC (*no copies of the probable causative mutation*)

EXPLANATION:

Every dog gets 2 copies of every gene - one from its mother and one from its father.

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 mother, and one that they got from their father.

Carriers, by definition, are dogs that have one copy of the mutated gene that they got from either their mother or their father 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.

- 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.
- 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.

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 a clear dog is bred to a non-carrier (clear) dog, none of their pups will be carriers and none will have EIC
- if a clear dog is bred to a carrier, about 1/2 of their pups will be carriers but none will have EIC

- if a clear dog is bred to an affected dog, all of their pups will be carriers, but none will actually have EIC.

Affected dogs have 2 copies of the mutation

- 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 (*having 2 copies of the mutation*) never exhibit any signs of EIC
- breeding one affected dog to another affected dog will result in all puppies having EIC.
- if an affected dog is bred to a carrier, about 1/2 of their pups will be carriers and ½ of their pups will be affected by EIC.
- if an affected dog is bred to a clear dog, all of their pups will be carriers, but none will actually have EIC

QUESTIONS?

Unfortunately, due to the overwhelming numbers of calls and emails about EIC it is no longer feasible for Dr. Taylor to return owner calls regarding clinical management of individual affected dogs. If veterinarians have specific questions about a dog with EIC that are not answered by this document they can email Dr. Taylor at sue.taylor@usask.ca. Every effort will be made to reply to email inquiries within 28 days.

Questions about sample collection or submission or test results should be directed to Katie Minor at the laboratory in Minnesota: minork@umn.edu