Evaluation of Dogs with Border Collie Collapse, Including Response to Two Standardized Strenuous Exercise Protocols

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ABSTRACT

Clinical and metabolic variables were evaluated in 13 dogs with border collie collapse (BCC) before, during, and following completion of standardized strenuous exercise protocols. Six dogs participated in a ball-retrieving protocol, and seven dogs participated in a sheep-herding protocol. Findings were compared with 16 normal border collies participating in the same exercise protocols (11 retrieving, five herding). Twelve dogs with BCC developed abnormal mentation and/or an abnormal gait during evaluation. All dogs had post-exercise elevations in rectal temperature, pulse rate, arterial blood pH, PaO2, and lactate, and decreased PaCO2 and bicarbonate, as expected with strenuous exercise, but there were no significant differences between BCC dogs and normal dogs. Electrocardiography demonstrated sinus tachycardia in all dogs following exercise. Needle electromyography was normal, and evaluation of muscle biopsy cryosections using a standard panel of histochemical stains and reactions did not reveal a reason for collapse in 10 dogs with BCC in which these tests were performed. Genetic testing excluded the dynamin-1 related exercise-induced collapse mutation and the V547A malignant hyperthermia mutation as the cause of BCC. Common reasons for exercise intolerance were eliminated. Although a genetic basis is suspected, the cause of collapse in BCC was not determined. (J Am Anim Hosp Assoc 2016; 52:281–290. DOI 10.5326/JAAHA-MS-6361)

Introduction

A disorder known as border collie collapse (BCC) is recognized as a cause of exercise intolerance in border collies throughout North America, Europe, and Australia.1,2 Dogs with BCC are normal at rest but occasionally develop incoordination and altered mentation after 5 to 15 min of strenuous exercise. This disorder has also been called exercise-induced hyperthermia, heat intolerance, exercise-induced collapse, and “the wobbles.”1,2 No consistent physical or biochemical abnormalities have been reported in affected dogs (S.T., unpublished data).3–5 Episodes of collapse are unpredictable and occur only during or immediately following strenuous exercise, making immediate veterinary evaluation difficult or impossible. Further complicating evaluation of affected dogs is the problem that many border collies refuse to participate in established strenuous exercise protocols retrieving balls, making it necessary to develop an alternative strenuous exercise protocol to evaluate sheep-herding dogs with BCC.

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BCC (border collie collapse); CBC (complete blood count); CK (creatine kinase); dEIC (dynamin-associated exercise induced collapse); ECG (electrocardiogram); EMG (electromyography); MH (malignant hyperthermia)

The online version of this article (available at www.jaaha.org) contains supplementary data in the form of three videos.

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This study describes the clinical and laboratory evaluation of dogs with BCC at rest and during and following completion of a standardized strenuous exercise protocol retrieving a ball or herding sheep and compares their findings with those of border collies without BCC performing the same exercise. The purpose of this study was to establish clinical and laboratory variables defining BCC in order to assist veterinary diagnosis of the disorder and to gain insight into the reason for collapse in affected dogs.

Materials and Methods

Normal Dogs
Sixteen client-owned border collies with normal capacity for exercise and no history of weakness or collapse were evaluated. All dogs participated regularly in agility competitions, flyball, or sheep-herding competitions or were working stock dogs. Dogs were determined to be healthy on the basis of history, physical examination, and laboratory evaluation (complete blood count [CBC], biochemical profile).

BCC Dogs
Thirteen client-owned border collies were referred to the investigating institution with a presumptive diagnosis of BCC. Each dog had experienced at least two observed episodes of exercise-induced weakness or collapse (two to >50 episodes, mean 7.8, median 2) beginning at 6 mo to 7 yr of age (median 2 yr), and their owners had completed a questionnaire describing the observed collapse episodes. Veterinary evaluation at rest had determined that systemic causes of collapse other than BCC were unlikely.

Evaluation of BCC Dogs at Rest
Complete physical examination (including orthopedic and neurologic examination), thoracic radiographs, lead 2 electrocardiogram (ECG), echocardiography, CBC, serum biochemical profile, serum cortisol, and acetylcholine receptor antibody titer were performed on each dog. Serum thyroxine was measured in six dogs.

Exercise
Each dog participated in a standardized strenuous exercise protocol, either retrieving a ball or herding sheep. This study was approved by the University of Saskatchewan’s Animal Health Research Board and adhered to the Canadian Council on Animal Care guidelines. Informed consent was obtained from owners of all dogs, and owners were present for their dog’s exercise.

Retrieving a Ball
Eleven normal dogs and six dogs with BCC repeatedly retrieved a tennis ball thrown 30 to 40 m for 10 min. Exercise was halted early if abnormalities of gait or mentation were apparent. The exercise consisted of short bursts of strenuous exercise interspersed with brief (<5 s) pauses as the ball was being surrendered and rethrown. Dogs typically sprinted at full speed to chase down the ball and returned to the handler at a slightly slower pace. Speed (meters per minute) was determined by calculating the distance run (number of retrieves x length of retrieval) divided by time measured using a stopwatch. Ambient temperature was recorded as each dog started exercising. Exercise and recovery were recorded on videotape for pace and gait analysis.

Herding Sheep
Five normal dogs and seven dogs with BCC performed a series of continuous short outruns and fetches of three sheep in an outdoor pen under the direction of their owners. Exercise was halted at 10 min or earlier if there were signs of gait or mentation abnormalities. Dogs typically ran at full speed in one direction around the perimeter of the pen a few meters behind the sheep, then passed the sheep to make them reverse direction and ran full speed in the opposite direction. Ambient temperature was recorded as each dog started exercising. Exercise and recovery were recorded on videotape for gait analysis.

Data and Sample Collection
Rectal temperature, pulse rate, reflexes, and a lead 2 ECG were assessed, and samples were collected for arterial blood gas, acid-base status, and plasma lactate and pyruvate concentrations before and immediately (within 1–2 min) after terminating exercise. A serum biochemical profile (including creatine kinase [CK] activity) was performed immediately after exercise. Rectal temperature, pulse rate, and limb reflexes were assessed 5, 10, 15, 30, 60, and 120 min after exercise. Serum CK activity was measured 120 min after concluding exercise in all BCC dogs and in the normal dogs herding sheep.

Measurement of Variables
Venous blood was collected into plain and EDTA-containing tubes. CBC variables were measured using an electronic counter, and a differential count was performed on a Wright Giemsa stained blood smear. Serum was separated within 30 min and analyzed immediately or held at −4°C for less than 24 hr before biochemical analysis using an automated analyzer. Blood from the femoral or dorsal metatarsal artery was collected into a heparinized syringe and analyzed immediately after collection using an in-house machine (retrieving protocol) or a hand-held analyzer (sheep...
herding protocol). Oxygen tension (PaO₂), carbon dioxide tension (PaCO₂), and pH were measured and corrected for rectal temperature, and bicarbonate concentration was calculated. Venous blood for lactate analysis was collected into sodium fluoride-containing tubes. Plasma separated within 30 min was frozen and stored at −20°C until analyzed using an immobilized enzyme membrane system (Comparative Neuromuscular Laboratory, Department of Pathology, University of California–San Diego, La Jolla, California). For pyruvate analysis, 1 ml of venous blood was collected into a tube containing 1 ml of 8% trichloracetic acid, mixed, and centrifuged for 10 min. The supernatant was removed and frozen at −20°C until analyzed. Pyruvate concentration was quantified by enzymatic determination, using lactate dehydrogenase, in a spectrophotometric assay (Comparative Neuromuscular Laboratory, Department of Pathology, University of California–San Diego, La Jolla, California).

Muscle Biopsy
At least 18 hr following participation in an exercise protocol, ten dogs with BCC (3/6 retrieving, 7/7 sheep herding) were routinely anesthetized (acepromazine 0.5 mg/kg IM, hydromorphone 0.1 mg/kg IM, propofol 4 mg/kg IV, isoflurane inhalation) and one-side electromyographic (EMG) recordings were made from proximal and distal appendicular muscles of the thoracic and pelvic limb and the temporalis, masseter, and lumbar epaxial muscles. A surgical biopsy of the vastus lateralis muscle was obtained, placed in a dry watertight container, and shipped at 4°C to the Comparative Neuromuscular Laboratory at the Department of Pathology, University of California–San Diego, La Jolla, California. Biopsies were flash-frozen in isopentane precooled in liquid nitrogen and processed by a standard panel of histological and histochemical stains and enzyme reactions including hematoxylin and eosin, modified Gomori trichrome, periodic acid-Schiff, myofibrillar ATPase reactions for fiber typing, succinic dehydrogenase, oil red O, acid and alkaline phosphatase, and esterase.

Examination of Known Mutations
DNA was isolated from whole blood of the 13 BCC dogs using the Gentra isolation protocol9 and stored at −20°C. All dogs were genotyped for the V547A ryanodine receptor (RYR1) mutation on canine chromosome 1 and the dynamin-1 (DNM1) mutation on canine chromosome 9 using standard published procedures.6,7

Analysis of Data
Clinical and laboratory findings before and following exercise were compared with established canine reference values. When post-exercise variables were outside established reference values for dogs at rest, the Mann Whitney U test was used to compare clinical and laboratory variable distributions post exercise between dogs with BCC and normal dogs performing the same standardized exercise protocol. The level of significance was P < .05 for all tests. Body temperatures of normal dogs and dogs with BCC participating in each exercise protocol were compared graphically and using the Fisher exact test to compare initial elevation and the timing of return to normal temperature.

Results

Evaluation of Normal Dogs at Rest
There were five males (four neutered) and 11 females (four spayed). Ages ranged from 1 to 7 yr (mean 2.9 yr), and body condition score was 2.5 to 3.5/5. Physical, orthopedic, and neurologic examinations and laboratory evaluation (CBC, biochemistry profile) were normal, except that seven dogs were mildly hyperglycemic (<6.8 mmol/L; reference range 3.3–5.6 mmol/L).

Evaluation of BCC Dogs at Rest
There were three females (two spayed) and ten males (three neutered). Age at the time of evaluation ranged from 1 to 8 yr (mean 4.5 yr). Body condition score was 2.5 to 3.5/5. Physical, orthopedic, and neurologic examinations were normal. Thoracic radiographs and ECG were normal in all dogs, and echocardiographic measurements were within reported breed-specific reference values, except for mild left atrial enlargement and mitral regurgitation in two dogs.8

All CBC variables were within reference range. Serum biochemical parameters including sodium, potassium, calcium, phosphorus, urea, creatinine, bilirubin, alkaline phosphatase, albumin, and total protein were within normal reference range for all dogs. One dog had a mildly elevated CK at rest (546 u/L; reference range 51–418 u/L). Two dogs were mildly hyperglycemic (<6.8 mmol/L; reference range 3.3–5.6 mmol/L). Serum acetylcholine receptor antibody titers were normal (<0.6 nmol/L) in all dogs. Resting serum thyroxine was normal in the six dogs tested (range 24–32 nmol/L; reference range 10–36 nmol/L), and resting serum cortisol was normal in all of the dogs (range 45–259 nmol/L; reference range 20–270 nmol/L).

Examination of Known Mutations
All 13 BCC dogs were negative for the infrequent V547A RYR1 mutation associated with malignant hyperthermia (MH) and negative for the R256L DNM1 mutation associated with a form of exercise-induced collapse found in Labrador retrievers and several other breeds.
Exercise—Retrieving Protocol

**Normal Dogs**

Ambient temperature was 13.6 °C–18.6 °C (median 16.1 °C). All 11 dogs participated in the retrieving drill for 10 min with no evidence of weakness, incoordination, or exercise intolerance during exercise or in the 120 min observation period that followed. They retrieved at an average speed of 130.1 +/- 6 m/min (100.6 to 153.4 m/min).

Nine of 11 dogs decreased their pace during the final 2–6 min of exercise secondary to delaying tactics like circuitous returns and refusal to surrender the ball.

**BCC Dogs**

Ambient temperature was 21.7 °C–22.9 °C (median 22.3 °C). All six of the BCC dogs participated in the retrieving drill for 10 min without developing abnormal gait or mentation. They retrieved at an average speed of 140 +/- 10 m/min (126 to 154 m/min), with all dogs exhibiting delaying tactics slowing their pace during the final 2–3 min of exercise. Five of the six BCC dogs exhibited a markedly abnormal gait following completion of retrieving exercise, and one dog exhibited very mild gait abnormalities (Table 1). Proprioception as assessed by response to knuckling and hopping was normal, and limb reflexes were normal.

The most severe abnormalities of gait and mentation were noted between 5 and 10 min after exercise. All dogs returned to normal within 10 to 30 min (median 22.5 min). Upon recovery, none exhibited muscular pain or stiffness, and all were alert and willing to resume retrieving.

Exercise—Sheep Herding protocol

**Normal Dogs**

Ambient temperature was 20°C–27°C (median 24°C). All five dogs participated in the herding protocol with no evidence of weakness, incoordination, or exercise intolerance during the 10 min of exercise or in the 120 min observation period. Dogs remained focused on the sheep and did not slow their pace during the exercise period.

**BCC Dogs**

Ambient temperature was 21°C–26°C (median 24.5°C). Four of the seven dogs had their exercise halted early (6.5 to 9.3 min) when they developed gait abnormalities (two dogs) and/or exhibited an abrupt loss in mental focus on the sheep (four dogs). All BCC dogs exhibited abnormal gait and mentation after completing the herding exercise (Table 1). Abnormalities were similar to, but more severe than, those observed in the retrieving BCC dogs (see Supplementary Video I, Video II, Video III). Proprioception was normal, as were limb reflexes. The most severe abnormalities of gait and mentation were noted 5 to 10 min after exercise. All dogs returned to normal within 20 to 30 min (median 30 min). Upon recovery, none exhibited muscular pain or stiffness, and all were alert and interested in the sheep.

Post Exercise Clinical Evaluation—All Dogs

All dogs were tachycardic and hyperthermic after exercise (Table 2). Femoral arterial pulses were strong and regular, and lead 2 ECG revealed sinus tachycardia. When dogs with BCC were compared with normal dogs within their exercise group, there was no difference in pulse rate. Body temperature post exercise was not different between normal dogs and dogs with BCC within each exercise group, but the dogs herding sheep were significantly more hyperthermic than the ball-chasing dogs (P = .001). Graphs created of the means of the sequentially measured body temperature of dogs completing each exercise protocol showed that the rate of temperature decline and the time to achieve normal body temperature after exercise did not differ between the dogs with BCC and the normal dogs within each exercise group (Figure 1).
Post Exercise Laboratory Evaluation—All Dogs

Arterial Blood Gas

Arterial blood pH was increased and PaCO2 was decreased in all dogs immediately after exercise (Table 2). Decreased serum bicarbonate, reflecting hyperlactatemia, was documented in all dogs. Serum bicarbonate was slightly lower in the BCC retrieving dogs than in the normal retrieving dogs (P = .03), but not significantly different between the normal and BCC dogs herding sheep.

Serum Biochemical Values

Many serum biochemical variables were slightly altered after exercise compared with pre-exercise values, but with the exception of creatinine, glucose, and CK activity, values remained within the normal reference range for all dogs (Table 2). Post-exercise serum creatinine values were within reference range in all normal dogs but were slightly elevated (≤151 umol/L; reference range 60–140 umol/L) in four BCC dogs. Seven of 13 BCC dogs and five of 16 normal dogs were mildly hyperglycemic (<8 mmol/L) after exercise, and one additional dog from each group was more significantly.
hyperglycemic (Table 2). Post-exercise serum CK activity was slightly increased over pre-exercise values in most dogs in both groups, but only BCC dogs had increases outside of the reference range immediately after exercise (two dogs) or 2 hr after exercise (four dogs). All increases in CK activity were mild (653; reference range 51–418 u/L) and not considered clinically significant (Table 2).

**Lactate, Pyruvate, and Lactate-to-Pyruvate Ratio**

The resting and post-exercise lactate and pyruvate concentrations and the lactate-to-pyruvate ratios in the BCC dogs were not consistently different from the values in normal dogs (Table 3). Lactate concentrations immediately post exercise were slightly higher in the dogs (normal and BCC) herding sheep than in the retrieving dogs (P = .046).

**Muscle Biopsy**

There were no abnormalities in temperature, blood pressure, and ventilation during general anesthesia. Needle EMG recordings were normal in all muscles in the ten affected dogs tested. Muscle biopsy specimens were normal from three dogs, all with clinically severe collapse from the sheep-herding group. Three dogs had a mild to moderate nonspecific increase in intramyofiber lipid droplets within some type 1 fibers, and four dogs had a mild to moderate predominance of type 1 fibers and an increased population of type 2C fibers compared with normal vastus lateralis muscle.9 These abnormalities were detected in dogs with mild and severe collapse from both protocols (retrieving and herding).

**Discussion**

There were no abnormalities in the clinical or laboratory evaluation of BCC dogs at rest that distinguished them from normal dogs. This evaluation was sufficient to eliminate many causes of exercise intolerance such as severe anemia, severe pulmonary disease, glucocorticoid deficiency, hypothyroidism, and acquired myasthenia gravis.9 Normal thoracic radiographs, echocardiography, and ECG pre- and post-exercise made cardiac causes unlikely. Normal muscle mass, normal pre-exercise gait and patellar reflexes, the ability to participate in moderate exercise, normal EMG, and relatively normal muscle biopsies eliminated inherited myopathies such as centronuclear myopathy, dystrophin deficient muscular...
<table>
<thead>
<tr>
<th>Variable</th>
<th>Dogs</th>
<th>Pre-Exercise</th>
<th>Post-Exercise</th>
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<tbody>
<tr>
<td>Lactate (mmol/L)</td>
<td>Normal border collies retrieving (11)</td>
<td>1.45 +/- 0.67</td>
<td>3.63 +/- 2.41</td>
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<td>1.10</td>
<td>3.67</td>
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<td>(0.8–2.94)</td>
<td>(1.12–5.7)</td>
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<td>Border collies with BCC retrieving (6)</td>
<td>1.00 +/- 0.25</td>
<td>5.02 +/- 1.43</td>
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<td>1.00</td>
<td>1.43</td>
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<td>(0.63–1.27)</td>
<td>(3.11–7.04)</td>
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<td>Normal border collies herding sheep (5)</td>
<td>1.88 +/- 0.62</td>
<td>9.56 +/- 4.96</td>
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<td>2.06</td>
<td>8.30</td>
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<td></td>
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<td>(1.16–2.62)</td>
<td>(4.98–18.04)</td>
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<td>Border collies with BCC herding sheep (7)</td>
<td>1.33 +/- 0.80</td>
<td>7.63 +/- 4.26</td>
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<td></td>
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<td>1.24</td>
<td>5.52</td>
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<td></td>
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<td>(0.61–3.00)</td>
<td>(4.89–15.89)</td>
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<tr>
<td>Pyruvate (mmol/L)</td>
<td>Normal border collies retrieving (11)</td>
<td>0.135 +/- 0.043</td>
<td>0.205 +/- 0.088</td>
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<td>0.124</td>
<td>0.216</td>
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<td>(0.079–0.210)</td>
<td>(0.074–0.324)</td>
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<td>Border collies with BCC retrieving (6)</td>
<td>0.120 +/- 0.040</td>
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<td>0.122</td>
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<td>(0.035–0.203)</td>
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<td>Normal border collies herding sheep (5)</td>
<td>0.087 +/- 0.040</td>
<td>0.205 +/- 0.062</td>
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<td>0.106</td>
<td>0.224</td>
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<td>(0.030–0.128)</td>
<td>(0.115–0.278)</td>
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<td>Border collies with BCC herding sheep (5 pre, 7 post)</td>
<td>0.240 +/- 0.271</td>
<td>0.279 +/- 0.032a</td>
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<td>0.128</td>
<td>0.283</td>
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<td>(0.079–0.720)</td>
<td>(0.242–0.340)</td>
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<td>Lactate/Pyruvate</td>
<td>Normal border collies retrieving (11)</td>
<td>11.29 +/- 5.01</td>
<td>19.21 +/- 8.91</td>
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<td>10.48</td>
<td>17.28</td>
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<td>(4.17–21.14)</td>
<td>(7.93–40.27)</td>
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<td>9.92 +/- 4.45</td>
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<td>9.40</td>
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<td></td>
<td></td>
<td>(5.10–18.00)</td>
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<tr>
<td></td>
<td>Normal border collies herding sheep (5)</td>
<td>26.42 +/- 13.85</td>
<td>51.87 +/- 33.01</td>
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<td></td>
<td>24.72</td>
<td>35.78</td>
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<td>(10.84–44.33)</td>
<td>(22.23–102.50)</td>
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<tr>
<td></td>
<td>Border collies with BCC herding sheep (5 pre, 7 post)</td>
<td>7.95 +/- 4.66a</td>
<td>26.93 +/- 12.74</td>
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<td>7.79</td>
<td>19.44</td>
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<td>(0.85–13.29)</td>
<td>(17.42–46.74)</td>
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Mean ± SD, median, and (minimum–maximum) of lactate and pyruvate concentrations and the lactate-to-pyruvate ratio before and immediately after exercise in 11 normal border collies retrieving a ball, 6 border collies with border collie collapse (BCC) retrieving a ball, 5 normal border collies herding sheep, and 7 border collies with BCC herding sheep.

*aSignificantly different from value in normal border collies assuming unequal variances.
dystrophy, or congenital nemaline rod myopathy. Acquired infectious or immune-mediated inflammatory myopathies were also excluded based on the normal clinical examination at rest, normal CK measurement, and the absence of inflammatory changes in the muscle. Abnormalities of glycolytic or oxidative metabolism that could result in poor exercise tolerance were ruled out by the absence of storage products in muscle fibers and normal lactate and pyruvate concentrations and lactate-to-pyruvate ratios at rest and after exercise in the BCC dogs. Biopsies from the vastus lateralis muscle of one affected retrieving dogs and three affected herding dogs did demonstrate a slight shift in the population of myofiber types from the expected mild type 2 predominance to a mild type 1 fiber predominance, although reference values specific to the border collie breed or for athletic dogs post-exertion have not been reported. All of the abnormalities observed in the muscle biopsies from dogs with BCC were considered minimal and unlikely to be related to their exercise intolerance.

All dogs evaluated were willing participants in the standardized strenuous exercise protocols, but normal and BCC-affected retrieving dogs consistently engaged in delaying tactics toward the end of exercise. This slowing of pace probably contributed to their lower post-exercise body temperature and lactate compared with the sheep-herding dogs. The sheep-herding dogs ran harder and were more focused on their task, and exercise had to be terminated before 10 min in four of seven dogs with BCC because of changes in mentation or gait. Owners consistently reported that the BCC episodes induced by both exercise protocols were less severe than those witnessed at home, probably because the investigators halted exercise at 10 min or earlier if subtle abnormalities were observed. Investigators also noticed that some dogs could be temporarily “called out” of their dazed state by applying leash or voice prompts; if left undisturbed, dogs with BCC had a tendency to exhibit more severe signs.

The features of BCC observed in these dogs were similar to those reported by owners in a large survey evaluating dogs with BCC (S.T., unpublished data). Abnormalities observed after exercise included upper motor neuron paresis and general proprioceptive ataxia in all four limbs, increased extensor tone and scuffing/knuckling of the pelvic limbs, crossing of the pelvic limbs, and exaggerated stepping and “stomping” with the thoracic limbs. Many of the dogs (10/13) also had truncal swaying and staggered or fell to the side, suggesting a balance problem, though none developed a head tilt or abnormal nystagmus. Most of the dogs evaluated (11/13) were mentally abnormal during BCC episodes, with mentation described by their owners and investigators as dull, disoriented, or distracted. Owners of the two dogs who had normal mentation after the exercise test both reported observing abnormal mentation during more severe episodes experienced at home. All these findings suggest that BCC is an episodic central neurologic disorder, not simply a manifestation of peripheral muscular weakness.

Most neurologic disorders cause constant, not intermittent, signs. The abnormal mentation, upper motor neuron paresis, and general proprioceptive ataxia observed in these dogs suggests an episodic diffuse central nervous system disorder. Exercise-induced paroxysmal dyskinesia can cause prolonged, repeatable episodes of abnormal posture and movement, but should not cause abnormal mentation. Clinical features of BCC episodes could be manifestations of a generalized non-convulsive seizure. Squinting eyes and rapid blinking occurred in one dog and has been recognized previously in dogs during BCC episodes (S.T., unpublished data). Repetitive eyelid blinking and photosensitivity are unusual signs in dogs but are a common automatism in several human non-convulsive epileptic disorders and in children with hyperventilation-induced non-epileptic “blank spells”. Inherited epilepsy is common in border collies, and dogs of this breed affected with epilepsy have an established tendency to develop severe tonic-clonic generalized seizures at a young age, with progression to cluster seizures and status epilepticus. None of the BCC dogs we studied had experienced a generalized convulsive seizure prior to evaluation, and none of the dogs for which we have follow-up (11/13) have had a seizure in the 3 yr since evaluation. The BCC episode phenotype seems to be very consistent, so if BCC is an exercise-induced seizure disorder, we suspect that it is a distinct disorder separate from inherited epilepsy in the breed.

Serum biochemical findings following exercise did not provide an explanation for BCC. Hypoglycemia and abnormalities of sodium, potassium, and calcium were not identified. There were mild increases in glucose and creatinine, as previously reported for normal dogs after strenuous exercise. Although a few dogs with BCC had mild (2× normal) elevations in serum CK activity immediately and 2 hr after exercise, the increases were not in the range characteristic of acute myonecrosis secondary to exertional rhabdomyolysis, MH, or heat stroke. It is possible that the measured elevations in CK activity would have been more pronounced 4 to 24 hr later, but elevations in CK are typically evident immediately post-exercise in myopathic disorders. Muscle biopsies taken approximately 18 hrs (retrieving dogs) or 8 days (herding dogs) after collapse were unremarkable.

Border collie collapse has been speculated to be a heat-related disease or even a manifestation of heat stroke or exercise-induced MH. Dogs with BCC recover quickly from their episodes of collapse without veterinary intervention and without significant
clinical or laboratory consequences, making a diagnosis of heat stroke unlikely. Heat stroke causing collapse in dogs is associated with prolonged hyperthermia, laboratory abnormalities, and high mortality, as many dogs succumb to the effects of endothelial injury, microvascular thrombosis, disseminated intravascular coagulation, and acute renal failure.\textsuperscript{25} DNA from the dogs with BCC did not contain the \textit{RYR1} mutation causing MH, and CK activity and rectal temperature during collapse and recovery were not different from normal dogs performing the same exercise, making MH very unlikely.

Body temperature after exercise was extremely elevated in the BCC dogs, but not different from normal border collies participating in the same exercise. The rate of body temperature decline also did not differ between the normal and BCC dogs in this study. Extreme elevations in body temperature following strenuous exercise similar to those reported here have been documented in normal dogs of multiple breeds.\textsuperscript{22,23,26}Hot environmental temperatures during exercise and overheating have been identified as possible triggers for collapse in dogs with BCC (S.T., unpublished data). Dogs with BCC should avoid prolonged intense exercise when the ambient temperature is hot, and owners should take measures to cool affected dogs during episodes of collapse.

All dogs participating in these strenuous exercise protocols developed significant respiratory alkalosis and metabolic acidemia, reflecting hyperventilation and strenuous anaerobic activity. Similar findings have been reported in normal exercising dogs of multiple breeds.\textsuperscript{22,23} Experimental hyperventilation (\textit{PaCO}_2 < 20 mmHg) of anesthetized dogs causes nervous system vasoconstriction and substantially decreases cerebral and spinal cord blood flow.\textsuperscript{27} Extreme hyperventilation may alter somatosensory input from the lower limbs, cause a loss of balance, and lower seizure threshold.\textsuperscript{28} Many of the normal and BCC dogs participating in both exercise protocols had post-exercise \textit{PaCO}_2 concentrations well below those reported to cause clinical signs experimentally, but there was no difference between the normal and BCC dogs.

Dynamin-associated exercise induced collapse (dEIC) and BCC both cause episodic collapse that is most likely to occur during exercise in hot weather, but the appearance of dogs during collapse is very different. While dogs with dEIC remain alert and have relatively flaccid but incoordinated pelvic limbs during collapse, dogs with BCC are more likely to be mentally abnormal, to demonstrate ataxia affecting all four limbs, and to have increased extensor tone in the pelvic limbs with scuffing or knuckling during walking.\textsuperscript{3,29} The \textit{DNM1} mutation causing dEIC was not found in the 13 dogs with BCC evaluated in this study.

Conclusion

This comprehensive clinical and metabolic evaluation of dogs with BCC was unsuccessful in determining the cause for collapse in affected dogs. The study does, however, provide strong evidence to discount many previously proposed explanations for collapse in BCC and provides a detailed clinical and clinicopathologic description of collapse episodes. At the present time, diagnosis requires recognition of the disorder by veterinarians and systematic elimination of all other causes of exercise intolerance.

\begin{itemize}
\item \textbf{VIDEO IA AND IB} Slow-motion video of an 8-year-old border collie affected by border collie collapse (BCC) 5 min following 10 min of strenuous exercise, exhibiting dazed mentation, ataxia in all four limbs, crossing pelvic limbs when walking, increased pelvic limb extensor tone, and scuffing and falling to the side.
\item \textbf{VIDEO II} Slow-motion video of a 2-year-old border collie during a border collie collapse (BCC) episode 5 min following exercise. The dog is mentally dull, takes exaggerated steps with the thoracic limbs, has increased extensor tone of the pelvic limbs and frequent scuffing of the thoracic and pelvic limbs while walking, and stumbles to the side.
\item \textbf{VIDEO III} Slow-motion video of a 19-month-old border collie 5 min after strenuous exercise. The dog is mentally dull, has exaggerated stepping or “stomping” of the forelimbs with occasional scuffing and increased tone, delayed protraction, and scuffing/knuckling of the pelvic limbs.
\end{itemize}

\textbf{FOOTNOTES}

\begin{itemize}
\item[a] Cell Dyn 3500; Abbott Diagnostics; Abbot Park, IL
\item[b] Hitachi 912; Roche Diagnostics; Indianapolis, IN
\item[c] Rapidlab 1200; Siemens Healthcare; Burlington, Ontario, Canada
\item[d] i-Stat Portable clinical analyzer, CG4+ cartridge; Abbott Point of Care, Inc.; Abbott Park, IL
\item[e] The Gentra Puregene\textsuperscript{TM} DNA Isolation kit; Qiagen; Hilden, Germany
\end{itemize}

\textbf{REFERENCES}

\begin{itemize}
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\item[6.] Roberts MC, Mickelson JR, Patterson EE, et al. Autosomal dominant canine malignant hyperthermia is caused by a mutation in the gene
encoding the skeletal muscle calcium release channel (RYR1).


