

Evaluation of blood cardiac troponin I concentrations obtained with a cage-side analyzer to differentiate cats with cardiac and noncardiac causes of dyspnea

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Objective—To determine whether measurement of blood cardiac troponin I (cTnI) concentrations with a cage-side analyzer could be used to differentiate cardiac from noncardiac causes of dyspnea in cats.

Design—Prospective, multicenter study.

Animals—44 client-owned cats with dyspnea and 37 healthy staff-owned cats.

Procedures—Affected cats were examined because of dyspnea; treatment was administered in accordance with the attending clinician's discretion. Cats were judged to have a cardiac or noncardiac cause of dyspnea on the basis of results of physical examination, thoracic radiography, and echocardiography. Blood cTnI concentrations were determined with a cage-side analyzer on samples collected within 12 hours after admission of affected cats. Concentrations for healthy cats were obtained for comparison.

Results—5 enrolled cats were excluded from the study because of concurrent cardiac and respiratory disease. Of the remaining 39 cats with dyspnea, 25 had a cardiac cause and 14 had a noncardiac cause. The 25 cats with a cardiac cause of dyspnea had a significantly higher blood cTnI concentration than did the 37 healthy cats or the 14 cats with a noncardiac cause of dyspnea.

Conclusions and Clinical Relevance—Measurement of cTnI concentrations with a cage-side assay in emergency settings may be useful for differentiating cardiac from noncardiac causes of dyspnea in cats. (*J Am Vet Med Assoc* 2014;244:425–430)

Respiratory emergencies in cats are challenging situations. Stabilization of these patients can often be a difficult task and is dependent on rapid assessment and appropriate initial interventions. Often, examinations and diagnostic testing prior to treatment are limited because even minimal stress can lead to decompensation or death. Dyspnea in cats may be attributable to many underlying causes, including asthma, obstruction of the upper airway (between the nares and larynx), neoplasia, infection, pleural space disease, and heart failure. A minimally invasive test that aids in the identification of patients with heart failure would be useful in this population. Results from previous studies^{1,2} suggest that the circulating cTnI concentration is helpful in distinguishing cats with dyspnea from those with underlying heart disease.

In human medicine, the primary reason for determining cTnI concentrations is for the diagnosis of isch-

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ABBREVIATIONS

cTnI	Cardiac troponin I
NPV	Negative predictive value
PPV	Positive predictive value

emic heart disease such as myocardial infarction, but troponin concentrations may be elevated and can result in cardiac injury in other disease processes, including myocardial contusions, congestive heart failure, cardiomyopathy, sepsis, and pulmonary embolism.^{3,4} Concentrations of cTnI may be elevated in cats with hypertrophic cardiomyopathy, myocardial contusions, hyperthyroidism, and renal insufficiency.⁵

Troponins are regulatory proteins involved in muscle contraction. There are 3 troponins (C, I, and T) that act as part of the contractile apparatus in cardiac and skeletal muscle cells. The cardiac isoforms of troponin I and T are specifically found in cardiac myocytes and are released into the bloodstream when damage to a cell results in a loss of membrane integrity. Assessment of concentrations of cTnI and cardiac troponin T has high sensitivity and specificity for myocardial damage, and they are considered to be useful biochemical markers for detection of cardiac cellular injury in humans.^{3,4}

Although few assays for cTnI have been specifically validated for use in veterinary medicine, it is generally

believed that human assays can be used for most species. The protein structure of cTnI is highly conserved among humans, dogs, and cats.⁶⁻⁹ Homology between the canine and feline genes and the human gene is 95% and 96%, respectively.⁷ Multiple cTnI assays have been developed by several manufacturers. Because of a lack of industry standardization, the reference range must be established for each assay, and values cannot be compared among the various assays.^{10,11}

Currently, availability of cardiac troponin testing in veterinary medicine is limited, sometimes requiring several days before results are provided. A rapid, affordable, and easily accessible cTnI test may help veterinarians identify patients with respiratory abnormalities attributable to cardiac disease and therefore patients that could benefit from administration of diuretic and cardiac-specific medications.

The purpose of the study reported here was to evaluate the use of a point-of-care multiuse analyzer to measure cTnI concentrations in cats with dyspnea. This analyzer could be used to perform cTnI analysis in 10 minutes with 16 to 22 μ L of blood. This rapid turnaround and small sample size would make the assay particularly appealing for clinicians dealing with dyspneic feline patients. The primary objective was to evaluate whether the measurement of cTnI concentrations with this analyzer could be useful in differentiating cardiac from noncardiac causes of respiratory abnormalities in cats. The secondary objective of the study was to assess precision of the assay.

Materials and Methods

Animals—A prospective, multicenter study was performed on client-owned cats with signs of respiratory distress referred to the emergency service at the New England Animal Medical Center, West Bridgewater, Mass, or the School of Veterinary Medicine at the University of Pennsylvania from November 2006 to June 2007. All cats evaluated for dyspnea during this time frame were considered eligible for inclusion in the study. Cats were excluded if they had a history of trauma during the period immediately preceding admission, if they had clear evidence of disease in the upper airway (between the nares and larynx), or if an echocardiogram could not be obtained. Cats also were excluded if they had evidence of both primary respiratory disease and cardiac disease.

Cats with congestive heart failure attributable to any underlying heart disease were included in the cardiac disease group. This determination was based on echocardiographic findings (evidence of structural heart disease), radiographic findings (left atrial enlargement in conjunction with a radiographic pulmonary pattern consistent with congestive heart failure), and response to treatment (ie, improvement in dyspnea after administration of furosemide). Multiple modalities were used to classify cats rather than radiographic findings alone because of the high amount of variation in findings for thoracic radiography of cats with heart failure.

The noncardiac disease group included cats with a definitive diagnosis of primary respiratory disease or cats without a definitive diagnosis of respiratory disease

but that were assessed to be free of cardiac disease on the basis of echocardiographic (no abnormalities detected in cardiac structure) and radiographic findings.

A control population that consisted of healthy cats owned by staff at the New England Animal Medical Center and the University of Pennsylvania School of Veterinary Medicine were included for comparison. This population of healthy cats was assessed to be free of heart disease on the basis of results of physical examination, thoracic radiography, and echocardiography.

For all cats, owner consent was obtained for all procedures performed. The study protocol was approved by the animal use and care committee at the University of Pennsylvania School of Veterinary Medicine.

Experimental procedures—After an initial evaluation, dyspneic cats were treated in accordance with the attending veterinarian's discretion. As soon as the cats were deemed stable enough to undergo venipuncture, 0.5 to 2 mL of blood was obtained and placed into appropriately sized tubes containing lithium heparin. Samples were collected from all dyspneic cats within 12 hours after admission, with most being obtained within the first 2 hours after admission. Blood samples were stored at room temperature (approx 21°C) and analyzed within 2 hours after collection.

Thoracic radiography and echocardiography were performed by a board-certified veterinary cardiologist or resident in a veterinary cardiology training program, and results were assessed to designate the cause of the dyspnea as cardiac or noncardiac in origin. Thoracic radiographs were also interpreted by a board-certified veterinary radiologist. When a veterinary cardiologist was not immediately available to perform echocardiography prior to euthanasia or discharge of an affected cat, ultrasonographic images were obtained by the attending veterinarian and were subsequently reviewed by a veterinary cardiologist to confirm the presence of heart disease.

A complete routine echocardiographic examination (2-D, M-mode, and Doppler) was performed in all enrolled cats. Echocardiography was performed in each cat with standard right long- and short-axis and left apical long-axis views.¹² Different ultrasonographic equipment^{a,b} was used at the 2 institutions.

Blood samples were collected from all healthy cats at the time of clinical examination. Similar to the procedure for blood samples obtained from cats with dyspnea, blood samples from healthy cats were stored at room temperature (21°C) and analyzed within 2 hours after collection.

cTnI analysis—Concentrations of cTnI were determined with blood samples stored in lithium heparin tubes. The test involved a 2-site ELISA, with a reportable range of 0 to 50.00 ng/mL. The lower limit of detection for the cage-side analyzer^c was 0.02 ng/mL.¹³ The reference range for healthy cats determined by use of this analyzer is 0 to 0.09 ng/mL, as reported by the manufacturer.¹⁴ Individual test cartridges^d were stored in a refrigerator and were warmed to room temperature (5 minutes at room temperature) prior to use. Each test required 16 to 22 μ L of blood. When enough blood was available, samples were assayed 3 times in immediate succession by the same observer for precision analysis.

Statistical analysis—To assess precision of the cage-side cTnI analyzer, samples were assayed in triplicate and examined by means of an intraclass correlation coefficient. Intraclass correlation coefficients > 0.9 were considered to have excellent precision. To assess diagnostic properties of the cTnI analyzer, sensitivity, specificity, PPV, and NPV (with 95% confidence intervals of various cutoff values) were calculated. To determine differences in cTnI concentrations between groups, the Kruskal-Wallis test was used. All analyses were performed with a statistical software package.^e Values were considered significant at $P < 0.05$.

Results

The study included 37 healthy cats ranging in age from 1 to 12 years (median age, 6 years). Eighteen (49%) were castrated males, and 19 (51%) were spayed females. Breeds represented included domestic shorthair ($n = 29$), domestic longhair (3), domestic medium-hair (2), Ragdoll (1), Siamese (1), and Egyptian Mau (1). The median concentration of cTnI in these healthy cats was 0.02 ng/mL (range, 0 to 0.17 ng/mL). Three healthy cats had cTnI concentrations greater than the reference range reported by the manufacturer. These 3 cats were all spayed females from 5 to 8 years of age. Two of these 3 cats had BUN concentrations within reference limits; the BUN concentration was not determined for the third cat.

The study also included 44 dyspneic cats. Of these 44 cats, 5 were excluded. Three were excluded from the study because of concurrent cardiac and respiratory disease. One cat (cTnI concentration, 2.12 ng/mL) had pleural effusion secondary to lymphoma and was found to have severe hypertrophic cardiomyopathy during echocardiography (the left atrial diameter was severely increased). The second cat (cTnI concentration, 0.59 ng/mL) had asthma and hypertrophic cardiomyopathy. The third cat (cTnI concentration, > 50.00 ng/mL) had a pulmonary mass visible on thoracic radiographs and severe cardiomyopathy during echocardiography. This cat was euthanized after an initial diagnostic evaluation, whereas the first 2 cats survived to discharge. None of these 3 cats were treated with diuretics.

Two other cats were excluded because of an inability to obtain an echocardiogram prior to discharge or euthanasia. One of these cats (cTnI concentration, 0.11 ng/mL) had an obstruction caused by a pharyngeal mass, and the other cat (cTnI concentration, 0.3 ng/mL) had a neoplastic pleural effusion suspected to be secondary to a destructive mass on a rib that was visible on radiographs.

Of the 39 remaining dyspneic cats, 25 had a cardiac cause (congestive heart failure) of dyspnea; these cats ranged in age from 2 to 17 years (median age, 9 years). Fifteen (60%) were castrated males, and 10 (40%) were spayed females. Twelve cats had hypertrophic cardiomyopathy (end-diastolic left ventricular wall thickness ≥ 6 mm), 3 cats had restrictive cardiomyopathy (end-diastolic left ventricular wall thickness < 6 mm and a restrictive mitral inflow pattern), 9 cats had an unclassified cardiomyopathy (end-diastolic left ventricular wall thickness < 6 mm and a normal or summated mitral inflow pattern), and 1 cat had high-grade second-degree

atrioventricular block. The median cTnI concentration in these cats was 1.68 ng/mL (range, 0.24 to 50.00 ng/mL). All of these cats had cTnI concentrations greater than those of the healthy cats. Sixteen (64%) of these cats had cTnI concentrations greater than the range for cats with a respiratory cause of dyspnea.

Fourteen cats had a noncardiac cause of dyspnea. They ranged in age from 11 months to 17 years (median age, 12 years). Eight were castrated males, 1 was a sexually intact male, and 5 were spayed females. The noncardiac causes of dyspnea included asthma ($n = 5$), noncardiogenic pleural effusion (2), pulmonary neoplasia (1), smoke inhalation (1), and undefined pulmonary disease (5). The median cTnI concentration in these cats was 0.16 ng/mL (range, 0.02 to 0.66 ng/mL). Eight of these cats had cTnI concentrations in the same range as that of the healthy cats, whereas 6 cats had concentrations within the same range as that of cats with a cardiac cause of dyspnea.

Range and median cTnI concentrations for the 3 groups of cats were plotted (Figure 1). Cats with cardiac disease had a significantly ($P < 0.001$) greater cTnI concentration (median, 1.68 ng/mL) than did healthy cats (median, 0.02 ng/mL) and cats with a noncardiac cause of dyspnea (mean, 0.16 ng/mL). There was an overlap of cTnI concentrations (0.24 to 0.66 ng/mL) between the 2 groups of cats with dyspnea. A cTnI concentration ≥ 0.24 ng/mL had 100% sensitivity and 57.1% specificity for determination of a cardiac cause of dyspnea. A cTnI concentration > 0.66 ng/mL had 72% sensitivity and 100% specificity for determination of a cardiac cause of dyspnea in these cats.

Results of the assessment performed for 3 cutoff values of cTnI concentrations to use in establishing sensitivity, specificity, PPV, NPV, and confidence intervals were summarized (Table 1). A receiver operating characteristic curve was created to determine whether blood cTnI concentrations were useful for differentiating cats with cardiac and noncardiac causes of dyspnea (Figure 2). The area under the curve was 0.94.

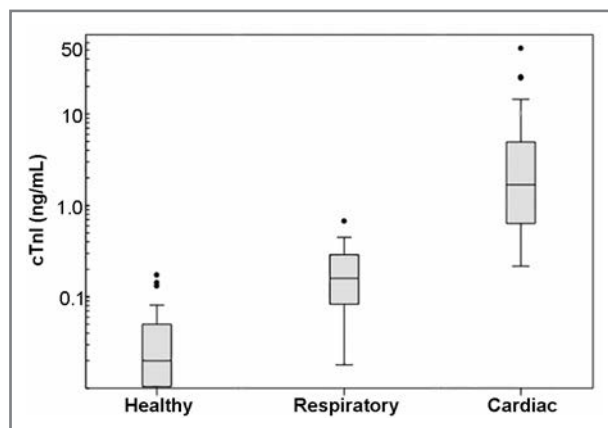


Figure 1—Box-and-whisker plots of cTnI concentrations for 37 healthy cats, 14 cats with dyspnea attributable to respiratory disease, and 25 cats with dyspnea attributable to cardiac disease. The top and bottom edges of each box represent the 75th and 25th percentiles, respectively; the horizontal line in each box represents the median value; the whiskers represent ≤ 1.5 times the interquartile range; and the circles represent outliers.

Table 1—Sensitivity, specificity, PPV, and NPV for determining a cardiac cause of dyspnea in cats at each of 3 cTnI concentrations.

cTnI concentration that identifies a cardiac cause of dyspnea (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥ 0.24	100 (86.3–100)	57.1 (28.9–82.3)	80.7 (62.5–92.6)	100 (63.6–100)
≥ 0.5	84.0 (63.9–95.5)	85.7 (57.2–98.2)	91.3 (72.0–98.9)	75.0 (47.6–92.7)
> 0.66	72.0 (50.6–87.9)	100 (76.8–100)	100 (81.5–100)	66.7 (43.3–85.4)

Values in parentheses are 95% confidence intervals. Values include the concentration (0.24 ng/mL) below which all cats did not have cardiac disease as a cause of signs of respiratory distress attributable to heart disease (sensitivity, 100%) and the concentration (0.66 ng/mL) above which all cats had cardiac disease as a cause of signs of respiratory distress (specificity, 100%).

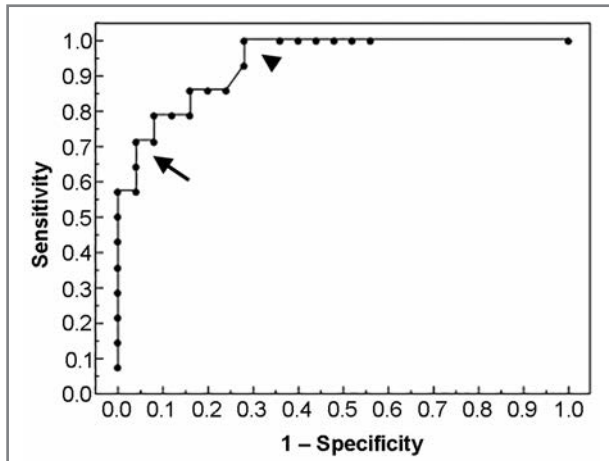


Figure 2—Receiver operating characteristic curve used to determine the usefulness of blood cTnI concentration to differentiate cats with cardiac versus noncardiac causes of dyspnea. The area under the curve is 0.94 (95% confidence interval, 0.82 to 0.98). The value below which no cats had cardiac disease as a cause of dyspnea (sensitivity, 100%; arrowhead) was 0.24 ng/mL, and the value above which none of the cats had respiratory distress attributable to cardiac disease (specificity, 100%; arrow) was 0.66 ng/mL.

Discussion

Analysis of results of the present study suggested that measurement of cTnI concentrations is a useful diagnostic test in cats evaluated for an unknown cause of dyspnea. All cats with cardiac disease in this study had blood cTnI concentrations ≥ 0.24 ng/mL. Of the 14 cats determined to have a noncardiac cause of dyspnea, 8 had cTnI concentrations within the same range as that of the healthy cats (≤ 0.17 ng/mL). Six of the cats with a noncardiac cause of signs of respiratory distress had concentrations > 0.24 ng/mL; these results were similar to those for cats with cardiac disease as a cause of dyspnea. None of the cats with noncardiac disease had concentrations > 0.66 ng/mL, whereas 16 of 25 (64%) cats with cardiac disease had concentrations > 0.66 ng/mL. On the basis of the results of this study, cTnI concentrations < 0.24 ng/mL can be used to rule out congestive heart failure as the cause of dyspnea, whereas concentrations > 0.66 ng/mL suggest a cardiac cause. Blood cTnI concentrations between 0.24 and 0.66 ng/mL were not useful for determining the cause of dyspnea; therefore, other diagnostic tests would be necessary to determine the underlying disease.

Results of the present study are consistent with those of previous studies in which investigators similarly found that plasma cTnI concentrations were useful in distinguishing cardiac from noncardiac causes of dyspnea. Investigators in 1 study¹ found that the 100% specificity threshold for determining noncardiac versus cardiac causes of dyspnea was 0.19 and 1.43 ng/mL, respectively. That study¹ revealed that a cTnI concentration ≥ 0.2 ng/mL had 100% sensitivity and 58% specificity for the diagnosis of cardiac disease, whereas a cTnI concentration > 1.42 had 58% sensitivity and 100% specificity for the diagnosis of cardiac disease. These sensitivity and specificity values are similar to those in the study reported here, although the 100% specificity threshold for identifying noncardiac or cardiac disease in the present study was 0.24 and 0.66 ng/mL, respectively. In other words, cats with a cTnI concentration < 0.24 ng/mL did not have dyspnea attributable to cardiac disease, and all cats with a cTnI concentration > 0.66 ng/mL had cardiac disease.

Investigators in another study² found that a cTnI concentration ≥ 0.81 ng/mL discriminated cats with cardiac disease with a sensitivity and specificity of 65.2% and 90.0%, respectively. They also found that the ranges for cTnI concentrations of cats with cardiac and noncardiac diseases overlapped, which was similar to the results of the present study. Different analyzers were used in those studies^{10,11}; therefore, absolute values cannot be compared with those of the study reported here. Owing to a lack of standardization between cTnI assays, the reference range must be established for each analyzer, and concentrations cannot be compared among different assays. However, it is interesting that the reference range for healthy cats generated in the present study (0 to 0.17 ng/mL) was essentially the same as that reported in another study¹⁵ that involved the use of a different analyzer. The analyzer used in the study reported here was a cage-side test with results available in minutes. Additionally, the blood volume requirement was small. Moreover, the low end of the range of detection is small enough to allow clinicians to discriminate between healthy and disease states, whereas the low end of the range of detection for some other tests is 0.2 ng/mL. The analyzer used in the present study is widely available to veterinary practices and will allow clinicians to obtain cTnI results within minutes after acquiring a blood sample from a patient.

Cardiac troponins are considered biomarkers of cell leakage and are released into the bloodstream af-

ter damage to cardiac myocytes results in a loss of cell membrane integrity.^{3,5} They are not markers of cardiac function. Cats with a history of trauma immediately preceding admission were excluded from the present study because myocardial contusions can result in elevated cTnI concentrations in cats.¹⁶ Also, cats with subclinical cardiac disease or renal disease may have elevated plasma cTnI concentrations.^{17,18} These points should be considered when interpreting elevated cTnI concentrations because cats with a noncardiac cause of dyspnea and concurrent subclinical cardiac or renal disease could be mistakenly thought to have congestive heart failure. This mistake in interpretation could have occurred for 3 cats in the present study. One cat had pleural effusion secondary to lymphoma (cTnI concentration, 2.12 ng/mL), the second cat had asthma (cTnI concentration, 0.59 ng/mL), and the third cat had a suspected mass in a lung (cTnI concentration, > 50.00 ng/mL). Cardiomyopathy was identified during echocardiographic evaluation in all 3 cats, and heart disease was considered severe in the cat with lymphoma and the cat with the suspected pulmonary mass. The cat with the suspected pulmonary mass was euthanized, but the other 2 cats survived to discharge. Neither of the surviving cats required treatment with diuretics, but without additional diagnostic testing, they could have been mistakenly classified as having congestive heart failure on the basis of cTnI concentrations alone and therefore may have been treated inappropriately. These cats were excluded from the statistical analysis because of concurrent cardiac and noncardiac diseases.

Limitations of the present study included the small sample size and the fact that not all causes of dyspnea were represented. There were no cats with confirmed heartworm disease, sepsis, or pulmonary hypertension included in this study. Pulmonary hypertension and sepsis can cause elevated cTnI concentrations in humans and therefore could possibly do the same in cats.^{19–21} Exclusion of cats with concurrent cardiac and noncardiac causes of dyspnea may also have affected the results. The 3 cats with concurrent disease had elevated cTnI concentrations. If these cats were included in the noncardiac disease population, then the specificity of the test would have been reduced. Owing to the possibility of this situation in practice, care must be exercised for interpretation of an elevated cTnI concentration. Another limitation is that renal function was not fully evaluated in some cats, although all cats had a BUN concentration within reference limits. Renal insufficiency can cause an increase in cTnI concentrations and therefore could have affected interpretation of the results. Investigators in 1 study¹⁸ found that 70% of cats with azotemic renal failure had elevated cTnI concentrations. This was thought to be secondary to occult cardiac injury or altered elimination of cTnI. Similarly, another limitation of the present study was that blood pressure and thyroid gland status were not evaluated in all cats. Therefore, it is possible that left ventricular hypertrophy was secondary rather than primary in some of the cats identified as having cardiac disease. However, because cats with systemic hypertension or thyrotoxicosis rarely develop congestive heart failure without concurrent primary heart disease, we believed this was unlikely.

Although most blood samples were analyzed immediately after collection, some samples were not tested within 30 minutes after collection (but all samples were analyzed within 2 hours after collection). This may have been a possible concern because the manufacturer recommended analyzing blood samples within 30 minutes after collection. However, investigators in a study¹³ in humans found that samples stored in a refrigerator or at room temperature for > 14 days had < 4% change in the cTnI concentration when assayed with the same analyzer that was used in the present study. Moreover, in another study²² in which investigators evaluated the in vitro stability of cTnI in samples maintained at room temperature, there was no significant change in cTnI concentration for 6 hours after sample collection.

Despite these limitations and on the basis of results of the present study, we suggest that measurement of cTnI concentrations with a cage-side analyzer may be a useful diagnostic tool for the evaluation of dyspneic cats. When interpreted in conjunction with other clinical findings, cTnI concentrations may add useful and timely information to the patient's database, which can aid in the differentiation of congestive heart failure from noncardiac causes of dyspnea in feline patients in emergency settings.

- a. Vivid I, 7 MHz transducer, General Electric Healthcare, Little Chalfont, Buckinghamshire, England.
- b. Sonos 7500, s12 transducer, Philips Medical Imaging, Andover, Mass.
- c. i-Stat 1 analyzer, Heska Corp, Loveland, Colo.
- d. Provided by Heska Corp, Loveland, Colo.
- e. SAS, version 9.2, SAS Institute Inc, Cary, NC.

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From this month's *AJVR*

Evaluation of a single intra-articular injection of autologous protein solution for treatment of osteoarthritis in horses

Alicia L. Bertone et al

Objective—To evaluate intra-articular autologous protein solution (APS) for the treatment of osteoarthritis in horses.

Animals—40 client-owned horses with naturally-occurring osteoarthritis.

Procedures—APS was generated from a dual-device system that concentrated plasma and WBC proteins and enriched platelet growth factors. Horses were randomly assigned to receive an intra-articular injection of 5 mL of saline (0.9% NaCl) solution (n = 20) or APS (20), exercised on a treadmill, and evaluated on the basis of lameness grades, kinetic gait analysis, joint circumference, and range of motion for 14 days. Horses that received saline solution were administered APS at termination of the study, and clients scored horses for lameness and discomfort before, 12 weeks after, and 52 weeks after the APS injection.

Results—The APS group had significant improvements in lameness grade, asymmetry indices of vertical peak force, and range of joint motion by 14 days, compared with baseline or control group values. No adverse effects associated with APS treatment were evident. Clients assessed lameness and comfort as improved at 12 and 52 weeks. The APS had greater likelihood (OR, 4.3 to 30.0) of a therapeutic response in horses with a lameness score < 4, < 10% vertical force asymmetry, or absence of marked osteophyte formation, subchondral sclerosis, or joint space narrowing. Concentration of interleukin-1 receptor antagonist in APS was 5.8 times that in blood.

Conclusions and Clinical Relevance—Intra-articular administration of APS can be considered an effective treatment option for equine osteoarthritis, with the potential for disease-modifying effects. (*Am J Vet Res* 2014;75:141–151)



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