Comparison of plasma cardiac troponin I concentrations among dogs with cardiac hemangiosarcoma, noncardiac hemangiosarcoma, other neoplasms, and pericardial effusion of nonhemangiosarcoma origin

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Objective—To determine whether plasma cardiac troponin I (cTnI) concentrations can be used to identify cardiac involvement in dogs with hemangiosarcoma, exclude cardiac hemangiosarcoma in dogs with noncardiac hemangiosarcoma, and identify cardiac hemangiosarcoma in dogs with pericardial effusion.

Design—Cohort study.

Animals—57 dogs (18 with confirmed [5 dogs] or suspected [13] cardiac hemangiosarcoma, 14 with confirmed hemangiosarcoma involving sites other than the heart [noncardiac hemangiosarcoma], 10 with pericardial effusion not caused by hemangiosarcoma, and 15 with noncardiac nonhemangiosarcoma neoplasms).

Procedures—Plasma cTnI concentration was measured, and thoracic radiography, abdominal ultrasonography, and echocardiography were performed in each dog. The cTnI concentration was compared among groups.

Results—Median plasma cTnI concentration in dogs with cardiac hemangiosarcoma was significantly higher than the concentration in each of the other groups. A plasma cTnI concentration > 0.25 ng/mL could be used to identify cardiac involvement in dogs with hemangiosarcoma at any site (sensitivity, 78%; specificity, 71%). A plasma cTnI concentration > 0.25 ng/mL could be used to identify cardiac hemangiosarcoma in dogs with pericardial effusion (sensitivity, 81%; specificity, 100%).

Conclusions and Clinical Relevance—The median plasma cTnI concentration was higher in dogs with cardiac hemangiosarcoma, compared with the median concentration in dogs with hemangiosarcoma at other sites, dogs with other neoplasms, and dogs with pericardial effusion not caused by hemangiosarcoma. The plasma cTnI concentration may be used to identify cardiac involvement in dogs with hemangiosarcoma and to identify cardiac hemangiosarcoma in dogs with pericardial effusion. (*J Am Vet Med Assoc* 2010;237:806–811)

Troponins are myofibrillar proteins intimately involved in myocardial contraction. Isoforms of troponin include C, I, and T. Blood concentrations of all isoforms increase in response to myocardial damage.[1–6] Although troponin I is present in skeletal muscle, cTnI has an additional sequence of 31 amino acids at its N-terminal portion.[7] The gene for cTnI, the inhibitory subunit of the troponin complex, has been cloned and sequenced for dogs, cats, and horses, and all 3 species have high homology with the sequence for the gene in humans and rodents.[8,9] Serum cTnI concentrations can reliably be measured by use of commercially available immunoassays in dogs, cats, and horses.[10]

Although there is no criterion-referenced standard kit for use in measurement of troponins in companion animals, a commercially available 2-site sandwich immunoassay that detects free and complexed cTnI has been validated for use in samples obtained from dogs.[8] The established reference interval for canine plasma concentrations of cTnI measured by use of that kit is from < 0.03 to 0.07 ng/mL, with the upper tolerance limit (ie, 0.07 ng/mL) at the 90th percentile with 95% confidence.[11]

In dogs, hemangiosarcoma most commonly involves the spleen, right atrium or atrial appendage of the heart, or subcutaneous tissues. Hemangiosarcoma has an aggressive biological behavior, metastatic disease is common, and the tumor often is disseminated within months after initial tumor detection. Because treatment recommendations are dependent on visible systemic extent of disease, thorough staging of patients with hemangiosarcoma includes thoracic radiography, abdominal

Abbreviations

CI	Confidence interval
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T

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ultrasonography, and echocardiography. Additional tests typically recommended for patients with hemangiosarcoma include a CBC, biochemical analysis, coagulation profile (prothrombin time and partial thromboplastin time), and urinalysis. Costs for staging can be high, and performance and interpretation of echocardiography, in particular, require experience and skill. Because the prognosis for patients with metastatic or multicentric hemangiosarcoma is worse than that for patients with surgically resectable hemangiosarcoma, accurate staging allows for a more informed decision-making process.[12]

Cardiac TnI is a sensitive and specific marker for myocardial damage; thus, it may have use as an indicator of cardiac involvement in patients with hemangiosarcoma. In 1 study,[2] evaluation of cTnI and cTnT concentrations in dogs with pericardial effusion revealed that dogs with cardiac hemangiosarcoma had significantly higher concentrations of cTnI than did dogs with idiopathic pericardial effusion. Concentrations of cTnT did not differ between dogs with hemangiosarcoma and those with idiopathic pericardial effusion.[2] Although size of the cardiac mass did not correlate with cTnI concentration, it was speculated that cTnI concentrations could be used to identify an otherwise clinically undetectable cardiac mass in dogs with pericardial effusion.

We hypothesized that plasma cTnI concentrations would be a sensitive indicator of the presence of a cardiac mass and that, through exclusion of cardiac involvement in dogs with noncardiac hemangiosarcoma, evaluation of cTnI concentrations would be a useful screening tool for dogs with known or suspected hemangiosarcoma. Furthermore, we sought to reexamine the sensitivity for plasma cTnI concentrations in detecting cardiac hemangiosarcoma in dogs with pericardial effusion.

Materials and Methods

Animals—Dogs were recruited prospectively for inclusion in the study on the basis of pericardial effusion or neoplasms. This protocol was approved by the University of Wisconsin-Madison Institutional Animal Care and Use Committee, and signed informed consent was obtained from each owner.

Procedures—Dogs were assigned to 1 of 4 groups on the basis of clinical signs and results of diagnostic tests (cytologic examination or examination of a biopsy specimen, thoracic radiography, abdominal ultrasonography, and echocardiography). The first group consisted of dogs with confirmed (via histologic diagnosis) or suspected (on the basis of characteristic echocardiographic findings of an infiltrative, mixed echogenic mass on the right atrium or right atrial appendage) cardiac hemangiosarcoma. The second group consisted of dogs with no evidence of pericardial effusion or cardiac mass lesions and that had histologically or cytologically diagnosed hemangiosarcoma at sites other than the heart (ie, noncardiac hemangiosarcoma). The third group consisted of dogs with pericardial effusion not caused by hemangiosarcoma as determined on the basis of examination of biopsy specimens or follow-up physical examination, echocardiography, or contact with the owner. The fourth group consisted of dogs with confirmed noncardiac neoplasms other than hemangiosarcoma. In some dogs, clinical data were accrued but assignment to a group was made after postmortem examination.

All echocardiograms were recorded by use of a 3-, 5-, or 7-MHz phased-array sector probe.[a] Dogs were restrained in right and left lateral recumbency on a table with a cutout to allow placement of the ultrasound probe on the lowermost (dependent) side of the thorax. An ECG was recorded simultaneously. Echocardiography was performed by one of the authors (HBK, RAH, or RLS), who were aware that these patients were being screened for cardiac mass lesions but had no additional information at the time of echocardiographic examination. At the conclusion of patient accrual, all echocardiograms were reviewed and group assignments were confirmed by one of the authors (RLS), who was unaware of the patient identity and tentative group assignment at the time of the review. Dogs were evaluated with 2-D echocardiography via the right parasternal, left parasternal, and left apical views. Irregular, heterogenic mass lesions attached to or invading the right atrium, right auricular appendage, or right atrioventricular junction were considered consistent with hemangiosarcoma. Detection of mass lesions in other locations during echocardiography was recorded, as was the presence or absence of pericardial effusion.

Measurement of cTnI concentrations—The plasma cTnI concentration was measured via a commercially available 2-site sandwich immunoassay.[b] This kit has been validated for measurement of cTnI concentrations in dogs.[8,10] A blood sample (2 to 4 mL) was collected from each dog. When pericardiocentesis was required, the blood sample was collected before that procedure was performed, except in 1 dog with a cardiac hemangiosarcoma. Blood samples were placed in heparinized collection tubes; tubes were centrifuged, and plasma was harvested within 2 hours after sample collection. Plasma was stored at 4°C until assayed; all cTnI assays were performed within 48 hours after sample collection.

Statistical analysis—Statistical analyses were performed by use of commercially available software.[c] Significance was set at values of $P < 0.05$ for all analyses. Median plasma cTnI concentration and median age of the 4 groups were compared by use of a Kruskal-Wallis test. Receiver operating characteristic curves were generated to determine the optimal cutoff value for the cTnI concentration used to detect cardiac involvement in dogs with hemangiosarcoma (by use of results for the first 2 groups [ie, dogs with cardiac hemangiosarcoma and dogs with noncardiac hemangiosarcoma]) and to determine the optimal cutoff value used to identify cardiac hemangiosarcoma in dogs with pericardial effusion (by use of results for the first and third groups [ie, dogs with cardiac hemangiosarcoma and dogs with pericardial effusion not caused by hemangiosarcoma]).

Results

Age, sex, and plasma cTnI concentrations for each group of dogs were summarized (**Table 1**; **Figure 1**). Notably, only a few dogs in this study had dilated cardiomyopathy or another identifiable relevant concurrent heart disease.

Table 1—Signalment and cTnI concentrations in 4 groups of dogs.

Group	Age (y) Median	Range	Sex	n	cTnI (ng/mL) Mean ± SD	Median	Range	Concurrent heart disease
Cardiac hemangiosarcoma (n = 18)	8.5	5–13	FS FI MN	10 1 7	10.7 ± 24.6	1	0–101.0	2 dogs: 1 with MR and TR and 1 with TR and AF (cTnI concentration, 6.7 and 0.1 ng/mL, respectively)
Noncardiac hemangiosarcoma (n = 14)	12	6–16	FS FI MN	9 1 4	0.6 ± 0.9	0.1	0–2.4	5 dogs: 1 with AS, 1 with endocardiosis, 1 with MR and TR, 1 with MR, and 1 with severe LVH (cTnI concentration, 0.1, 1.0, 2.3, 0.1, and 0.2 ng/mL, respectively)
Pericardial effusion not attributable to hemangiosarcoma (n = 10)	9	6–12	FS MN	4 6	0.1 ± 0.1	0.1	0–0.2	3 dogs: 1 with MR and TR, 1 with TVD, and 1 with MR and TR (cTnI concentration, 0, 0.1, and 0.2 ng/mL, respectively)
Other neoplasms (n = 15)	10	5–12	FS MN MI	7 7 1	0.1 ± 0.06	0	0–0.2	3 dogs: 1 with MR, TR, and PH; 1 with MR, TR, LVH, and PH; and 1 with MR (cTnI concentration, 0.1, 0.2, and 0.1 ng/mL, respectively)

AF = Atrial fibrillation. AS = Aortic stenosis. FI = Female, sexually intact. FS = Female, spayed. LVH = Left ventricular hypertrophy. MI = Male, sexually intact. MN = Male, neutered. MR = Mitral valve regurgitation. n = Number of dogs. PH = Pulmonary hypertension. TR = Tricuspid valve regurgitation. TVD = Tricuspid valve dysplasia.

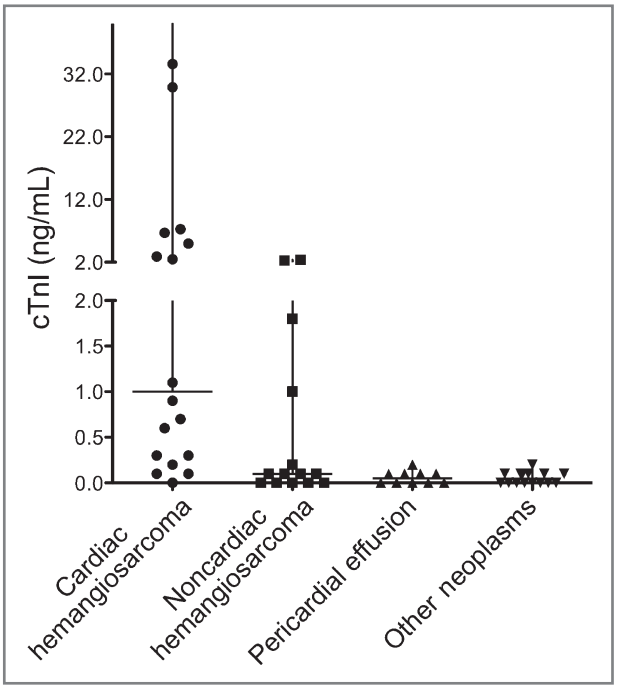

Figure 1—Concentrations of cTnI in 4 groups of dogs (cardiac hemangiosarcoma [n = 19], noncardiac hemangiosarcoma [14], pericardial effusion not attributable to hemangiosarcoma [10], and other neoplasms [15]). Horizontal lines represent median values, and vertical lines represent the range. One outlying value (101.0 ng/mL) for the cardiac hemangiosarcoma group was outside the range and is not shown.

The first group had cardiac hemangiosarcoma and consisted of 18 dogs with confirmed (via histologic diagnosis [5 dogs]) or suspected (on the basis of characteristic echocardiographic findings of an infiltrative, mixed echogenic mass on the right atrium or right atrial appendage [13]) cardiac hemangiosarcoma. There were 6 Golden Retrievers or Golden Retriever–crossbred dogs, 4 Labrador Retrievers or Labrador Retriever–crossbred dogs, 1 Australian Cattle Dog, 1 Beagle-crossbred dog, 1 Borzoi, 1 Boxer, 1 Bullmastiff, 1 German Shepherd Dog, 1 German Shorthair Pointer, and 1 Greyhound. Lung metastases were identified during radiographic or postmortem examination in 2 dogs, and noncardiac (ie, visceral) hemangiosarcoma was identified in 5 dogs. An echocardiographically identified mass lesion was detected in all dogs, and pericardial effusion was identified in 16 of 18 dogs. Postmortem examination was performed on 5 dogs; cardiac involvement was confirmed during postmortem examination in these 5 dogs. Of 18 dogs with confirmed or suspected hemangiosarcoma, 14 had a plasma cTnI concentration > 0.25 ng/mL (Figure 1).

The second group had noncardiac hemangiosarcoma and consisted of 14 dogs (6 Golden Retrievers, 2 German Shepherd Dogs, 1 Beagle, 1 Cocker Spaniel, 1 Greyhound, 1 Labrador Retriever–crossbred dog, 1 Pointer, and 1 Standard Poodle). A histologic diagnosis of hemangiosarcoma was made in 12 dogs; hemangiosarcoma was diagnosed in the remaining 2 dogs on the basis of clinical signs and results of physical examination, ultrasonography, and cytologic examination. Eight dogs had hemangiosarcoma in the spleen; 2 of the 8 dogs had metastasis (1 with metastases to subcutaneous tissues and to other abdominal viscera and the other with metastases only to other abdominal viscera) at the time the cTnI concentration was measured. Five dogs had hemangiosarcoma in subcutaneous tissues, 1 dog had the liver as the only identified site of the tumor, and 1 dog had the mediastinum and lungs as the only identified sites of the tumor. A complete postmortem examination was performed on 3 dogs in this group (a dog with involvement of mediastinal and lung tissues [plasma cTnI concentration, 0 ng/mL], a dog

with splenic involvement and metastasis [plasma cTnI concentration, 2.4 ng/mL], and a dog with only splenic involvement [plasma cTnI concentration, 0.1 ng/mL]). The plasma cTnI concentration was > 0.25 ng/mL for 4 of 14 dogs in this group (Figure 1).

The third group had pericardial effusion of nonhemangiosarcoma origin and consisted of 10 dogs (3 Golden Retrievers, 2 Labrador Retrievers, 1 Australian Cattle Dog, 1 English Bulldog, 1 Foxhound, 1 German Shorthaired Pointer, and 1 Saint Bernard). Nine dogs had a histologic diagnosis (5 with pericarditis, 1 with restrictive pericarditis, 1 with a melanoma, 1 with a chemodectoma, and 1 with a mesothelioma). One dog had idiopathic pericardial effusion on the basis of the follow-up examination at least 6 months after initial admission and pericardiocentesis with no recurrence of pericardial effusion detected via echocardiography. Postmortem examination was performed on 2 dogs in this group; 1 had a melanoma (plasma cTnI concentration, 0.1 ng/mL), and the other one had a chemodectoma (plasma cTnI concentration, 0.2 ng/mL). No dogs in this group had a plasma cTnI concentration > 0.3 ng/mL (Figure 1).

The fourth group had neoplasms other than hemangiosarcoma and consisted of 15 dogs (3 sighthounds [1 Greyhound, 1 Italian Greyhound, and 1 Whippet), 2 Labrador Retrievers, 2 Rottweilers, 1 Border Collie, 1 Boxer, 1 Brittany Spaniel, 1 Bulldog, 1 Fox Terrier, 1 Golden Retriever, 1 Samoyed, and 1 Shar Pei). A histologic diagnosis was made in 10 dogs (3 with an oral melanoma, 2 with concurrent benign splenic and hepatic changes, 2 with an apocrine gland adenocarcinoma of the anal sac, 1 with an osteosarcoma, 1 with a mast cell tumor, and 1 with a fibrosarcoma). Cytologic examination was only used to diagnose lymphoma in 2 dogs, multiple mast cell tumors in 1 dog, and a metastatic perianal adenocarcinoma in 1 dog. A probable chemodectoma was diagnosed in 1 dog on the basis of characteristic echocardiographic findings (a homogenous, smooth mass lesion positioned at the heart base in close proximity to the great vessels [plasma cTnI concentration, 0.1 ng/mL]). None of the dogs in this group underwent postmortem examination.

Age did not differ significantly among groups. Median plasma cTnI concentration of dogs with cardiac hemangiosarcoma was significantly higher than that for the other 3 groups of dogs; the median plasma cTnI concentration did not differ significantly among those 3 groups of dogs.

Plasma concentrations of cTnI for the first 2 groups of dogs (ie, 18 dogs with cardiac hemangiosarcoma and 14 dogs with noncardiac hemangiosarcoma) were used to determine the optimal cutoff value for use in determining cardiac involvement in dogs with hemangiosarcoma. There was a significant ($P = 0.006$) area under the curve (0.79). Use of a plasma cTnI concentration > 0.25 ng/mL for diagnosing cardiac involvement in dogs with hemangiosarcoma yielded a sensitivity of 78% (95% CI, 52% to 94%) and specificity of 71% (95% CI, 42% to 92%). A plasma cTnI concentration ≥ 2.45 ng/mL could be used to reliably identify cardiac involvement in dogs with hemangiosarcoma of other organs (specificity, 100%; 95% CI, 77% to 100%), although the sensitivity was low (44%; 95% CI, 22% to 69%).

Similarly, the optimal cutoff value for use in detection of cardiac hemangiosarcoma in dogs with pericardial effusion was determined by use of dogs in the first and third groups (ie, 18 dogs with cardiac hemangiosarcoma and 10 dogs with pericardial effusion of nonhemangiosarcoma origin). Two dogs with cardiac hemangiosarcoma were excluded because no pericardial effusion was detected; so results represented analysis of data for 26 dogs. There was a significant ($P < 0.001$) area under the curve (0.93; 95% CI, 0.83 to 1.00). Use of a plasma cTnI concentration > 0.25 ng/mL to detect cardiac hemangiosarcoma in dogs with pericardial effusion yielded a sensitivity of 81% (95% CI, 54% to 96%) and specificity of 100% (95% CI, 69% to 100%).

Discussion

Troponin concentrations are a sensitive and specific marker of myocardial damage in dogs.[1,3–6,13,14] Although cTnI concentration is an excellent indicator of myocardial damage and is correlated with severity of cardiomyopathy in most studies[3,6,13] in dogs, elevated concentrations are not associated with a specific underlying cause because the cTnI concentration is elevated in dogs with both cardiac and noncardiac dyspnea.[15] However, investigators in a number of studies[1–6,8,10,11,14,16–23] conducted to evaluate a variety of diseases in dogs have reported that troponin concentrations are prognostic. An elevated cTnI concentration is associated with a poorer prognosis in dogs with gastric dilatation–volvulus[5,14] and is significantly higher in dogs with hemangiosarcoma and pericardial effusion than in dogs with nonneoplastic pericardial effusion.[2] Higher cTnI concentrations are associated with a poorer prognosis in dogs with leptospirosis or babesiosis.[15,20,21] Concentrations of both cTnI and troponin T have been evaluated as markers for myocardial damage secondary to doxorubicin treatment.[4,22] In 7 research dogs given doxorubicin via an intracoronary route, serum cTnI concentrations increased during the 8-week period after administration; however, peak cTnI concentrations did not correlate with functional changes.[22]

Evaluation of 44 dogs with naturally occurring cancer treated with doxorubicin to a maximum cumulative dose of 150 mg/m^2 revealed that serum cTnI concentration did not predict cardiac outcome.[22] A prospective evaluation of cTnT revealed increased cTnI concentrations in dogs with congestive heart failure and skeletal muscle trauma and dogs that received doxorubicin at a dosage of 180 mg/m^2.[4]

In a study[2] conducted to compare cTnI and cTnT concentrations in dogs with confirmed cardiac hemangiosarcoma or idiopathic pericardial effusion, investigators reported that median cTnI concentrations were significantly higher in dogs with cardiac hemangiosarcoma (2.77 ng/dL) than in dogs with idiopathic pericardial effusion (0.05 ng/dL). Clinically, this has useful implications in that small cardiac masses can be difficult to identify during echocardiography and evaluation of cTnI concentrations could be used to differentiate idiopathic pericardial effusion from neoplasia-induced pericardial effusion.

In the study reported here, plasma cTnI concentrations were compared among dogs with cardiac heman-

giosarcoma, noncardiac hemangiosarcoma, pericardial effusion of nonhemangiosarcoma origin, and neoplasms other than hemangiosarcoma. Although a weakness of this study is the lack of histopathologic findings to confirm cardiac hemangiosarcoma, all of the dogs classified with cardiac hemangiosarcoma had the characteristic echocardiographic appearance of hemangiosarcoma, and the diagnosis in the other groups was confirmed on the basis of results of cytologic or histologic examination. Another potential weakness was concurrent heart disease in each group of dogs. Clinically normal dogs have a median cTnI concentration of 0.03 ng/mL (range, 0.01 to 0.15 ng/mL) with an upper 95th percentile of 0.11 ng/mL, whereas dogs with mitral valvular disease have a higher median cTnI concentration of 0.11 ng/mL (range, 0.01 to 9.53 ng/mL), and dogs with subaortic stenosis have a median cTnI concentration of 0.08 ng/mL (range, 0.01 to 0.94 ng/mL).[3] Although there were small numbers of dogs in each group in the study reported here, there were similar numbers of dogs with concurrent heart disease in each group. Despite the aforementioned issues, the findings for the study reported here support the evaluation of cTnI concentrations as a screening tool for cardiac involvement in dogs with noncardiac hemangiosarcoma (in the viscera or subcutaneous tissues) and for identification of cardiac hemangiosarcoma in dogs with pericardial effusion.

Although evaluation of plasma cTnI concentrations proved promising for use in identifying cardiac involvement in dogs with hemangiosarcoma, 4 dogs with noncardiac hemangiosarcoma had plasma cTnI concentrations that exceeded our suggested cutoff value (false-positive results). One of these dogs had confirmation of a lack of cardiac involvement and an apparently normal heart during postmortem examination, but postmortem examination was not performed on the other 3 dogs. Elevated plasma cTnI concentrations in all 4 of these dogs may have been caused by occult nonneoplastic myocardial disease that was undetectable during routine echocardiography, but the clinical course of these dogs did not vary from the expected course of the condition as determined on the basis of the fact these dogs had neoplasms and none of them had signs compatible with heart failure. The presence of neoplasia alone did not appear to cause an increase in plasma cTnI concentrations in dogs with neoplasms other than hemangiosarcoma; thus, it is unlikely that some other aspect related to the neoplastic process or the presence of nondetected concurrent neoplasms led to increases in plasma cTnI concentrations in dogs with noncardiac hemangiosarcoma. These findings suggest that although a severe increase in plasma cTnI concentration (> 2.45 ng/mL) can reliably be used to identify cardiac involvement when used as a screening test, dogs with moderate cTnI concentrations (0.07 to ≤ 2.45 ng/mL) may benefit from further diagnostic evaluation with echocardiography.

Four dogs (3 of which had pericardial effusion) with cardiac hemangiosarcoma had plasma cTnI concentrations (0, 0.1, 0.1, and 0.2 ng/mL, respectively) less than the suggested cutoff value. Postmortem examination and histologic examination were not performed to confirm cardiac hemangiosarcoma in any of these 4 dogs. Another 3 dogs with hemangiosarcoma had plasma cTnI concentrations higher than the recommended upper limit for dogs (0.07 ng/mL) and would have been identified as abnormal in a screening situation. Again, a postmortem examination was not performed on these 3 dogs, so it is possible the heart lesions did not infiltrate the myocardium, despite the echocardiogram review that confirmed probable hemangiosarcoma status. Although echocardiography cannot provide a tissue diagnosis of hemangiosarcoma, it appears anecdotally that there is wide clinical use of lesion appearance and location to identify probable cardiac hemangiosarcoma in dogs with pericardial effusion.

Results of the present study confirm the suggestion that evaluation of cTnI concentrations may be useful in identifying cardiac hemangiosarcoma in dogs with pericardial effusion. Furthermore, findings in this study suggest that there is likely to be cardiac hemangiosarcoma when a dog with pericardial effusion has a plasma cTnI concentration > 0.25 ng/mL. This finding may be useful in patients in which echocardiography is not feasible; however, samples should be collected before pericardiocentesis to avoid confounding the results through inadvertent cardiac trauma.

Evaluation of cTnI concentrations may be useful when evaluating dogs with pericardial effusion or dogs with known hemangiosarcoma for the presence of cardiac hemangiosarcoma. A plasma cTnI concentration > 0.25 ng/mL indicates that cardiac hemangiosarcoma is likely in dogs with pericardial effusion, and a plasma cTnI concentration > 2.45 ng/mL indicates that cardiac involvement is likely in dogs with hemangiosarcoma. Echocardiography is recommended in dogs with pericardial effusion or known hemangiosarcoma of noncardiac origin that have a plasma cTnI concentration > 0.07 ng/mL and < 0.25 ng/mL.

a. GE Vivid 7, General Electric Medical System, Waukesha, Wis.
b. Stratus, Dade-Behring Inc, Newark, Del.
c. GraphPad Prism, version 5.0b for Mac, GraphPad Software, San Diego, Calif.

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