Evaluation of serum cardiac troponin I concentration in dogs with renal failure

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Objective—To determine whether dogs with renal failure have higher serum cardiac troponin I (cTnI) concentrations than healthy dogs.

Design—Case-control study.

Animals—31 dogs with renal failure and 51 healthy dogs.

Procedures—Serum concentrations of creatinine and cardiac troponin I, urine specific gravity, and systolic arterial blood pressure were measured for all dogs. Dogs underwent a standardized physical examination, and any dog with evidence of cardiovascular disease or other nonrenal disease was excluded from final analyses. Dogs were considered to be in renal failure when the serum creatinine concentration was ≥3.0 mg/dL, urine specific gravity was between 1.007 and 1.030, and renal failure had been clinically diagnosed.

Results—Dogs with renal failure had significantly higher serum cTnI concentrations (median, 0.35 ng/mL) than did healthy dogs (0.20 ng/mL). The renal failure group also had a significantly higher median systolic blood pressure (156 mm Hg) than did healthy dogs (138 mm Hg), although serum cTnI concentration was not correlated with systolic blood pressure in dogs with renal failure. There was no significant difference in age between dogs with renal failure and healthy dogs, but dogs with renal failure had significantly higher serum creatinine concentration and lower urine specific gravity.

Conclusions and Clinical Relevance—Although dogs with renal failure did not have overt clinical signs of cardiac disease, they had high serum cTnI concentrations, which may have been associated with subclinical cardiovascular disease. The cause of the high serum cTnI concentration in these dogs requires additional investigation. (J Am Vet Med Assoc 2009;234:767–770)

Measurement of the serum concentration of cardiac troponin is considered standard for detection of cardiac myocyte damage in humans. Troponins are muscle proteins that are released from damaged myocytes into the circulation, and cardiac-specific isoforms are biomarkers for heart damage in many animal species, including humans, rodents, and dogs.1 In people with an acute coronary syndrome, a high serum cardiac troponin concentration is a sensitive and specific indicator for diagnosis, is of prognostic value, and predicts the benefit of invasive treatment.2,3 Nevertheless, concerns about the specificity of measurement of serum cardiac troponin concentration for diagnosis of acute coronary syndromes have developed because of increasing evidence that values may increase in association with nonischemic cardiac disease and even noncardiac diseases.4 There is interest in the application of serum cardiac troponin measurements for diagnostic purposes in dogs, yet evaluation of the performance of such a measurement for the diagnosis of spontaneous cardiac disease in domestic species is in the early stages.5,6

The ability of several types of serum cTnI assays to detect various types of heart disease in dogs has been evaluated in several studies7–12; however, there is little information on the association of high serum troponin concentration with primary disease processes that do not involve the heart.13 In humans, serum cardiac troponin concentration is high in patients receiving high-dose chemotherapy and those with septicemia and cerebrovascular disease.14 The potential for patients with renal failure to have a high serum cardiac troponin concentration without primary cardiac disease that requires clinical intervention is considered a critical diagnostic dilemma in human medicine.15–20 Given the high prevalence of renal insufficiency in veterinary patients, this potential for misclassification must be clarified in dogs if serum cardiac troponin concentration is to be useful in clinical situations. The purpose of the study reported here was to determine whether dogs with renal failure but without evidence of heart disease have a higher serum cTnI concentration than healthy dogs.

Abbreviation

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<th>cTnI</th>
<th>Cardiac troponin I</th>
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Materials and Methods

Case dog selection—Dogs with renal failure were recruited from the patient population at the University of Minnesota Veterinary Medical Center from June 2006 through December 2007. Dogs were only included when their serum creatinine concentration was ≥ 3.0 mg/dL and urine specific gravity was between 1.007 and 1.030 within 24 to 48 hours after physical examination and collection of blood samples. Dogs were excluded when concurrent nonrenal disease was evident in their history or in the results of physical examination or laboratory tests. Dogs were classified as having acute renal failure when 2 or more of the following conditions existed: clinical signs of renal failure for < 7 days, > 50% decrease in serum creatinine concentration within 7 days before evaluation at the hospital, PCV within the reference range when evaluated for inclusion in the study, good to obese body condition, and histologic diagnosis of acute renal failure at necropsy. Dogs were classified as having chronic renal failure when 2 or more of the following conditions existed: azotemia for > 14 days; clinical signs of renal failure for > 7 days; history of weight loss; ultrasonographic diagnosis of small, irregular kidneys; and histologic diagnosis of chronic renal failure at necropsy. Medical records were reviewed to identify the cause of the renal failure, when possible.

Control dog selection—Healthy dogs were recruited from the Community Practice Service of the Veterinary Medical Center and from faculty, students, and staff. Dogs were only included in this group when they had no history of chronic health problems, were not receiving medications other than those recommended for parasite control, and had unremarkable results of physical examination. Dogs were excluded when their serum creatinine concentration was > 1.5 mg/dL (reference range, 0.6 to 1.6 mg/dL).

Procedures—After consent was obtained from dog owners, all dogs were screened for evidence of cardiac disease by the attending clinician or one of the investigators by use of a standardized physical examination designed for the study. For the measurement of systolic arterial blood pressure, dogs were positioned in lateral recumbency. An appropriately sized cuff was positioned between the carpal and elbow joints. A Doppler probe was used to locate the arterial pulse signal. A sphygmomanometer was used to inflate the cuff until the pulse signal could no longer be detected, and then the cuff was deflated until the signal was detected again. The systolic arterial blood pressure was determined by averaging the 3 most consistent of several readings collected at least 10 seconds apart.

A 3-mL blood sample was collected from a jugular, cephalic, or lateral saphenous vein of each dog for determination of serum concentrations of creatinine and cTnI. Creatinine concentration was measured within 12 hours after sample collection; an aliquot of serum was frozen at −80°C for measurement of cTnI concentration at a later time. Urine was collected from each dog via midstream catch during natural voiding, catheter, or cystocentesis for the determination of specific gravity. Blood pressure measurement and collection of blood and urine samples were performed within a 24-hour period. All procedures were approved by the University of Minnesota Institutional Animal Care and Use Committee.

Laboratory testing—Serum creatinine concentration was determined by use of the modified Jaffe technique with an automated analyzer. Serum cTnI concentration was measured with a solid-phase, chemiluminescent immunometric assay that uses a monoclonal murine antibody against troponin I. Analytic sensitivity in human serum was reported by the manufacturer as 0.2 ng/mL at the beginning of the study but was revised to 0.1 ng/mL mid study; the calibration range extended to 180 ng/mL. Four pools of canine serum (mean concentration range of the pools, 0.31 to 2.26 ng/mL) were used to evaluate measurement precision. Serum pools were divided into aliquots and immediately frozen. Each pool was assayed in duplicate, twice a day for 10 days. Within-run (< 5.0%) and total assay (< 5.6%) coefficients of variation for all pool measurements were < 6.0%.

For the purposes of statistical analysis, values that were lower than the detection limit of the cTnI assay were reported as being equal to the originally published detection limit of 0.2 ng/mL that was reported by the manufacturer at the beginning of the study to prevent a change in reporting procedures from biasing the study. Urine specific gravity was determined by refractometry.

Statistical analysis—Continuous data (ie, age, serum creatinine and cTnI concentrations, serum specific gravity, and systolic arterial blood pressure) were reported as median (range), and the measurements for the control and renal failure groups were compared with the Mann-Whitney U test. Categoric data (ie, proportions of males vs females in each group) were compared with the Fischer exact test. Linear regression analysis (to assess linear correlations) and the Spearman rank correlation coefficient (to assess nonlinear correlations) were used to evaluate the relationship between systolic arterial blood pressure and serum cTnI concentration in dogs with renal failure. Statistical significance was defined as P < 0.05. Ninety-five percent reference intervals were calculated for serum cTnI concentration by use of values from healthy dogs.

Results

Animals—For the control group, 31 healthy dogs representing 23 breeds were recruited, of which the median age was 6 years (range, 0.5 to 12 years). Twenty-two dogs were female, and 29 were male. For the renal failure group, 53 dogs with a laboratory diagnosis of renal failure were initially recruited. Of these 53 dogs, 7 were excluded because a heart murmur was detected during hospitalization and 15 were excluded because of concomitant nonrenal disease (ie, aortic insufficiency, arthritis, cholangiohepatitis, chronic bronchitis, diabetes mellitus, epilepsy, hypoadrenocorticism, hyperadrenocorticism, immune-mediated hemolytic anemia, inflammatory bowel disease, lymphoma, pancreatitis, pemphigus foliaceus, or transitional cell carcinoma). Of the remaining 31 dogs with renal failure, 21 breeds were represented and the
median age was 6 years (range, 1 to 13 years). Nineteen dogs were female, and 12 were male.

Nine of the 31 (29%) dogs in the renal failure group were classified as having acute renal failure. In 6 of the 9 dogs, no cause for the acute renal failure could be determined. In 1 dog, acute renal failure was attributed to consumption of raisins; in 2 others, it was attributed to leptospirosis. The remaining 22 (71%) dogs were classified as having chronic renal failure, with the exception of 1 dog in which there was insufficient information for classification. For 11 of 21 (52%) dogs with a diagnosis of chronic renal failure, no cause could be determined. Six dogs with chronic renal failure had a diagnosis of protein-losing nephropathy (3 were suspected of having Lyme disease), 1 had a necropsy diagnosis of glomerular amyloidosis, 1 had a necropsy diagnosis of membranoproliferative glomerulonephritis, and 2 had a diagnosis of congenital renal dysplasia.

A necropsy was performed on 4 dogs in the renal failure group (1 dog with acute renal failure and 3 dogs with chronic renal failure). One of these dogs had a grossly normal heart with no results of histologic evaluation reported. In the remaining 3 necropsy reports, the following cardiac lesions were described: 1 dog had multifocal fibrosis with lymphocytic infiltration of surrounding tissue, another had endocardiosis, and a third had focal hemorrhagic infarct with acute necrotizing myocarditis and necrotizing arteritis.

Results of a Fisher exact test indicated that the distribution of sex did not differ significantly ($P = 0.17$) between groups. Age was also similar between groups. Systolic arterial blood pressure in dogs with renal failure was significantly ($P < 0.001$) higher, compared with that in control dogs (Table 1); however, there was no significant ($P = 0.13$) linear correlation between serum cTnI concentration and systolic arterial blood pressure in dogs with renal failure. Furthermore, results of the Spearman rank correlation analysis did not support a nonlinear correlation between serum cTnI concentration and systolic arterial blood pressure ($P = 0.37$).

Laboratory results—Serum cTnI concentration was significantly ($P < 0.001$) higher in dogs with renal failure, compared with that in control dogs. Of the 51 healthy dogs, only 3 had a serum cTnI concentration that exceeded the detection limit of the assay (0.22, 0.27, and 0.40 ng/mL), whereas 23 of the 31 dogs with renal failure had a value that exceeded the detection limit. The 95% reference interval for serum cTnI concentration in healthy dogs was calculated to be 0.20 to 0.26 ng/mL, and 20 dogs with renal failure had a serum cTnI concentration that exceeded the upper reference limit.

Discussion

The present study was designed to test the hypothesis that dogs with renal failure have a higher serum cTnI concentration than healthy dogs. Results supported this hypothesis: 66% of dogs with renal failure had a serum cTnI concentration that exceeded the upper reference limit. All dogs in the study were considered free of clinical cardiovascular disease on the basis of clinical history and results of a standardized cardiovascular physical examination. Dogs with renal failure had higher systolic arterial blood pressure than did healthy dogs; however, there was no significant correlation between the hypertension and the high serum cTnI concentration. A study in humans also failed to identify a relationship between arterial blood pressure and serum troponin concentration.

Our study was not designed to identify etiologic factors that might cause the increase in serum cTnI concentration; however, the results may have been attributable to an increased incidence of subclinical cardiac disease in dogs in the renal failure group, compared with the incidence in the control group, or to impaired clearance of cTnI or its metabolites as a result of a decrease in renal function. Although results of histologic evaluations of the heart were only available for 3 dogs with renal failure, it is worth mentioning that all 3 dogs had cardiac lesions. These limited data suggested that the potential for dogs with renal failure to be at risk for developing cardiac disease should be investigated.

Approximately 80% of dogs with renal insufficiency in our study and a similar proportion in another retrospective study of dogs with renal failure had a high serum cTnI concentration. In comparison, approximately 7% to 18% of humans with renal failure without primary cardiac disease reportedly have a high serum cTnI concentration. The underlying cause of the high value in these situations remains unclear and is the subject of continued investigation. Several mechanisms have been proposed to explain this phenomenon, including subclinical ischemic damage to cardiac myocytes, myocardial remodeling or left ventricular hypertrophy, and uremic pericarditis or myocarditis. Failure of clearance of cTnI from the blood also may contribute to a high serum cTnI concentration in humans with renal insufficiency, although this hypothesis is questioned because improvement in renal function after transplant does not alter this value, nor is there a consistent relationship between serum creatinine concentration and the frequency or magnitude of the increase in cardiac troponin concentration in blood.

The results of the case-control study reported here support those of another retrospective study, in which an increase in serum troponin concentration was detected in dogs with azotemia. Compared with our study, the other study involved different serum cTnI analyzers, a decision limit of 0.2 ng/mL for that analysis, and

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<th>Variable</th>
<th>Healthy dogs</th>
<th>Dogs with renal failure</th>
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<tbody>
<tr>
<td>Systolic arterial blood pressure (mm Hg)</td>
<td>138 (76–180)</td>
<td>156 (110–204)</td>
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<tr>
<td>Serum creatinine concentration (mg/dL)</td>
<td>1.0 (0.6–1.4)</td>
<td>5.3 (3.0–11.6)</td>
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<td>Urine specific gravity</td>
<td>1.040 (1.013–1.065)</td>
<td>1.012 (1.007–1.027)</td>
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<td>Serum cTnI concentration (ng/mL)</td>
<td>0.20 (0.20–0.40)</td>
<td>0.35 (0.20–0.95)</td>
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For all variables, values are significantly ($P < 0.05$) different between groups.
different inclusion criteria (including a lower serum creatinine value for indicating renal failure [\(> 2.0 \, mg/dL \, vs \geq 3.0 \, mg/dL \, in \, the \, present \, study\)]. Regardless of the important methodologic differences that preclude direct comparison of data, both studies confirmed a high serum cTnI concentration in dogs with renal failure. This suggests that comorbid diseases such as renal failure may confound diagnostic interpretation of high serum cTnI concentration as an indicator of clinical heart disease. Clinically important increases in serum cTnI concentration have also been detected in dogs with gastric dilatation-volvulus, parvoviral infection, blunt chest trauma, and pyometra.

Our study had limitations that must be considered when interpreting the results. The most important limitation was that echocardiography and histologic evaluation of the heart were not performed in healthy dogs or dogs with renal failure, so one cannot determine whether a high serum cTnI concentration in dogs with renal failure is attributable to underlying cardiac disease that might have been detectable by use of echocardiographic or histologic methods. Furthermore, the existence of subclinical cardiac disease in the healthy control dogs in the present study cannot be excluded, particularly given that 3 control dogs appeared to have a higher serum cTnI concentration than most of the other control dogs. This also threatened the validity of our reference interval values because we could not be certain that all dogs were free of cardiac disease.

Ideally, it would have been preferable to have echocardiographically evaluated all dogs; however, such an action was beyond the scope of the present study. Thus, we could not specifically define any increased risk of cardiovascular disease in dogs with renal failure, compared with the risk in apparently healthy dogs, or the types of cardiac disease that were associated with renal disease in the dogs of our study. Nevertheless, we could conclude that dogs with renal failure were more likely to have a higher serum cTnI concentration than healthy dogs, even when those dogs did not have clinical signs of heart disease. Additional research is required to determine whether high serum cTnI concentration reflects primary concurrent cardiac disease or myocardial damage that develops secondary to renal disease and to evaluate the clinical importance in the management of affected dogs.

References


c. Olympus AU-400e, Center Valley, Pa.
d. Immulite 1000 Troponin I kit, Siemens, Los Angeles, Calif.