Clinical utility of serum N-terminal pro-B-type natriuretic peptide concentration for identifying cardiac disease in dogs and assessing disease severity

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Objective—To determine whether serum N-terminal pro-B-type natriuretic (NT-proBNP) concentration could be used to identify cardiac disease in dogs and to assess disease severity in affected dogs.

Design—Cross-sectional study.

Animals—119 dogs with mitral valve disease, 18 dogs with dilated cardiomyopathy, and 40 healthy control dogs.

Procedures—Serum NT-proBNP concentration was measured with an ELISA validated for use in dogs. Results of physical examination, thoracic radiography, echocardiography, and serum biochemical analyses were recorded for dogs with cardiac disease.

Results—Serum NT-proBNP concentration was significantly higher in dogs with cardiac disease than in control dogs, and a serum NT-proBNP concentration > 445 pmol/L could be used to discriminate dogs with cardiac disease from control dogs with a sensitivity of 83.2% and specificity of 90.0%. In dogs with cardiac disease, serum NT-proBNP concentration was correlated with heart rate, respiratory rate, echocardiographic heart size, and renal function. For dogs with cardiac disease, serum NT-proBNP concentration could be used to discriminate dogs with and without radiographic evidence of cardiomegaly and dogs with and without congestive heart failure.

Conclusions and Clinical Relevance—Results suggested that serum NT-proBNP concentration may be a useful adjunct clinical test for diagnosing cardiac disease in dogs and assessing the severity of disease in dogs with cardiac disease. (J Am Vet Med Assoc 2008;232:1496–1503)

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Clinical assessment of heart disease in dogs has traditionally relied on evaluations of history and results of physical examination, cardiopulmonary auscultation, and thoracic radiography. Methods with greater quantitative value, such as echocardiography, generally require additional expertise to perform and interpret as well as additional financial cost to the owner. Thus, a biomarker that could be used to help detect cardiac disease in dogs and assess disease severity would be useful clinically.

B-type natriuretic peptide is a potential biomarker of cardiac disease. The major stimulus for release of BNP by the heart is an increase in intracardiac hydrostatic pressure. The peptide is released into the circulation as a precursor molecule that is rapidly cleaved by serum proteases into 2 fragments: C-terminal BNP and NT-proBNP. In circulation, BNP increases natriuresis, urine production, and renal blood flow; enhances diastolic function; decreases systemic vascular resistance; and decreases filling pressure in the heart. Thus, BNP has biological effects that counter those of angiotensin and aldosterone and provides a natural check to activation of this system. In humans, serum BNP concentration is commonly used to help differentiate potential causes of acute dyspnea, stratify severity of heart failure, and assess the likelihood of clinically important cardiovascular outcomes, such as death. In addition, serum BNP concentration can guide treatment in patients with heart failure and detect occult cardiac disease in high-risk populations, such as the elderly. Currently, measurement of serum BNP concentration is...
recommended as one of the first steps in the evaluation of human patients suspected to have heart failure, along with physical examination, thoracic radiography, and electrocardiography.13

Serum C-terminal BNP concentration is typically high in dogs with heart disease, regardless of whether they have congestive heart failure.14–16,19 Until recently, however, measurement of serum BNP concentration has been limited by lack of an ELISA specific for dogs.17 Serum BNP concentration can be evaluated by measuring either C-terminal BNP or NT-proBNP concentration, and because of biochemical differences between the 2 molecules, there are potential advantages and disadvantages associated with either strategy. Because the half-life of C-terminal BNP is on the order of minutes, measurement of serum C-terminal BNP concentration is better suited to detection of acute changes in neurohormonal activation or volume status. In contrast, NT-proBNP has a longer half-life, and serum NT-proBNP concentration would therefore be expected to have less moment-to-moment variability.18–20 Studies21,22 in human patients indicate that clinical utilities of these 2 BNP assays are similar, but NT-proBNP is typically present in higher concentrations, and measurement of serum NT-proBNP concentration does not require specialized collection or handling protocols, making measurement of serum NT-proBNP concentration more attractive.

The purposes of the study reported here were to determine clinical utility of serum NT-proBNP concentration for detection of cardiac disease in dogs and as an indicator of disease severity. We hypothesized that dogs with MVD or DCM would have significantly higher serum NT-proBNP concentrations than would healthy dogs without evidence of cardiac disease and that serum NT-proBNP concentration would correlate with radiographic, echocardiographic, and biochemical indices of disease severity.

Materials and Methods

Dogs—Dogs with acquired myxomatous MVD or idiopathic DCM examined between November 2006 and June 2007 at the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania, The Animal Medical Center (New York), Cummings School of Veterinary Medicine, or Advanced Veterinary Care Center (Lawndale, Calif) were considered for enrollment in the study. Dogs were eligible for inclusion only if the diagnosis could be confirmed echocardiographically. A diagnosis of MVD was made on the basis of echocardiographic detection of thickened or prolapsed mitral valve leaflets and color-flow Doppler echocardiographic evidence of mitral regurgitation. A diagnosis of DCM was made on the basis of echocardiographic detection of eccentric left ventricular hypertrophy, high left ventricular end-systolic dimension, and low fractional shortening.

Dogs with BUN concentration > 70 mg/dL and dogs with concurrent diseases that confounded the diagnosis of MVD or DCM (eg, cardiac tamponade, congenital heart disease, endocarditis, neoplasia, chronic obstructive pulmonary disease, and heartworm disease) were excluded from the study.

For comparison, a control group of healthy dogs recruited from local pet owners, hospital employees, and veterinary students was also included in the study. Dogs were considered healthy on the basis of results of physical and echocardiographic examinations and serum biochemical testing.

Study procedures were approved by the institutional animal use and care committees of each participating institution. Owner consent was obtained for all dogs included in the study.

Assessment of cardiac disease severity—A serum biochemical profile was performed in all dogs with MVD or DCM enrolled in the study. In addition, left ventricular dimension at end-diastole, left ventricular dimension at end-systole, aortic dimension, and left atrial dimension were measured by means of standard echocardiographic techniques,23,24 and thoracic radiography was performed. Vertebral heart size was measured on the left or right lateral radiographic projection by the attending cardiologist as described.25,26 For Cavalier King Charles Spaniels, a vertebral heart size < 11.7 was considered normal.27 For all other breeds, a vertebral heart size ≤ 10.5 was considered normal.

A clinical cardiac scoring system adapted from the International Small Animal Cardiac Health Council system28 was used to classify dogs with MVD or DCM. Class Ia was defined as subclinical heart disease without radiographic evidence of cardiac enlargement. Class Ib was defined as subclinical heart disease with radiographic evidence of cardiac enlargement. Class II–compensated was defined as congestive heart failure that had been controlled by medications for at least 12 hours after the initial clinical or radiographic examination. Class II–active was defined as mild signs of congestive heart failure (eg, mild increase in respiratory rate and effort, exercise intolerance, and coughing) in a dog in which the sample for measurement of serum NT-proBNP concentration was collected while clinical signs and radiographic abnormalities consistent with pulmonary edema or effusion were evident. Class IIIa was defined as overt, severe signs of congestive heart failure (eg, severe respiratory distress, profound weakness, and syncope) that were treated on an outpatient basis. Class IIIb was defined as severe signs of congestive heart failure that required hospitalization.

Measurement of serum NT-proBNP concentration—Venous blood samples were collected into plain evacuated glass tubes that did not contain any additives. Samples were centrifuged within 60 minutes after collection, and serum was stored at –20°C prior to overnight shipment at 4°C for analysis. Serum NT-proBNP concentration was determined with a commercially available canine-specific NT-proBNP assay.29 The assay was a sandwich ELISA incorporating 2 polyclonal ovine anti-canine NT-proBNP antibodies targeted to amino acids 25 through 42 (capture antibody) and 1 through 22 (detection antibody). The detection antibody was conjugated to horseradish peroxidase, and NT-proBNP was detected colorimetrically at a wavelength of 450 nm. Interassay coefficients of variation were 7.1%, 8.6%, and 8.2%, and intraassay coefficients of variation were 6.4%, 8.4%, and 7.1% at NT-proBNP concentrations of 360, 667, and 1,744 pmol/L, respectively. Samples were
assayed in duplicate at a central laboratory by personnel blinded to the patient diagnosis, and the mean value of the 2 determinations was used for all analyses.

Statistical analysis—Data were summarized as mean and SD or median and IQR (25th to 75th percentile). The lowest reported value for the assay was < 180 pmol/L. For purposes of statistical analysis, values reported as < 180 pmol/L were coded as 179 pmol/L. The Student t or Mann-Whitney test was used to compare serum NT-proBNP concentration between healthy control dogs and dogs with heart disease (MVD or DCM), and the Kruskal-Wallis test followed by the Dunn multiple comparison test was used to compare serum NT-proBNP concentration among heart disease groups. The Spearman method was used to test for correlations between serum NT-proBNP concentration and murmurs, heart and respiratory rate, serum biochemical findings, and radiographic and echocardiographic heart size. Multivariate stepwise linear regression was performed to identify continuous variables associated with serum NT-proBNP concentration; P value cutoffs for entry into and removal from the multivariate model were < 0.05 and > 0.10, respectively. All analyses were performed with standard software.

Values of P < 0.05 were considered significant.

Results

Dogs—One hundred nineteen dogs with MVD, 18 dogs with DCM, and 40 healthy control dogs were included in the study (University of Pennsylvania, 88; The Animal Medical Center, 57; Tufts University, 25; Advanced Veterinary Care Center, 12). Twenty-one of the 119 (18%) dogs with MVD were of mixed breeding, 15 (13%) were Cocker Spaniels, and 11 (9%) were Cavalier King Charles Spaniels; the remaining dogs represented 40 other breeds. Five of the 18 (28%) dogs with DCM were Doberman Pinschers, 3 (17%) were Boxers, 2 (11%) were Irish Setters, and 2 (11%) were Mastiffs; the remaining dogs represented 6 other breeds. Thirteen of the 40 (33%) control dogs were of mixed breeding, 4 (10%) were Great Danes, and 4 (10%) were Golden Retrievers; the remaining dogs represented 13 other breeds. Sex distribution (dogs with MVD: 9 sexually intact males, 12 females; dogs with DCM: 4 sexually intact males, 4 females; dogs with heart disease: 13 males, 22 females) did not differ significantly among groups.

A cardiac murmur was detected in all 119 dogs with MVD (median murmur grade, 4; range, 1 to 5) and in 13 of the 18 dogs with DCM (median murmur grade, 2; range, 1 to 5). Thirty-two (27%) dogs with MVD had dyspnea, 9 (8%) had a gallop rhythm, and 9 (8%) had ascites. Nine of the dogs with DCM had dyspnea, 5 had a gallop rhythm, and 4 had ascites. Fifty-six of the 119 (47%) dogs with MVD were considered class I (10 class Ia and 46 class Ib), 24 (20%) were considered class II (14 compensated and 10 active), and 39 (33%) were considered class III (22 class IIIa and 17 class IIIb). Four of the 18 (22%) dogs with DCM were considered class I (1 class Ia and 3 class Ib), 6 (33%) were considered class II (4 compensated and 2 active), and 8 (44%) were considered class III (4 class IIIa and 4 class IIIb). Physical examination, radiographic, and echocardiographic findings of dogs with MVD or DCM were recorded (Table 2).

Serum NT-proBNP concentration—For the control dogs, median serum NT-proBNP concentration was 290 pmol/L (Figure 1). The 90th and 95th percentile values were 478 and 598 pmol/L, respectively. Median serum NT-proBNP concentration for the male control dogs (249 pmol/L) was not significantly different (P = 0.26) from median concentration for the female control dogs (310 pmol/L), and there was no evidence that serum NT-proBNP concentration in the control dogs was correlated with age (P = 0.61), weight (P = 0.48), BUN concentration (P = 0.71), or serum creatinine concentration (P = 0.53). Median serum NT-proBNP concentration for purebred control dogs (n = 27; median, 318 pmol/L; IQR, 233 to 426 pmol/L) was significantly (P = 0.033) higher than the median concentration for mixed-breed control dogs (n = 13; median, 231 pmol/L; IQR, 179 to 330 pmol/L).

Median serum NT-proBNP concentrations in dogs with MVD (median, 1,188 pmol/L; IQR, 579 to 2,756 pmol/L) and in dogs with DCM (median, 1,748 pmol/L; range, 992 to 2,621 pmol/L) were significantly (P < 0.001) higher than the median concentration in control dogs (Figure 1). However, concentration was not significantly different between dogs with MVD and dogs with DCM.

Table 1—Baseline descriptive characteristics of 177 dogs in which serum NT-proBNP concentration was measured.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 40)</th>
<th>MVD (n = 119)</th>
<th>DCM (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>7.0 (4.3–8.0)</td>
<td>11.0 (9.0–12.0)</td>
<td>9.0 (7.0–11.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>19.9 (8.5–30.5)</td>
<td>10.0 (7.7–13.7)</td>
<td>10.6 (9.0–14.1)</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>16.5 (14.0–21.0)</td>
<td>22.5 (15.8–32.0)</td>
<td>20.0 (14.9–32.0)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2 (1.0–1.3)</td>
<td>1.0 (0.8–1.3)</td>
<td>1.1 (0.9–1.4)</td>
</tr>
</tbody>
</table>

Data are given as median (IQR). *Significantly (P < 0.05) different from value for control dogs. †Significantly (P < 0.05) different from value for dogs with MVD.

Table 2—Physical examination, radiographic, and echocardiographic characteristics of 137 dogs with MVD or DCM in which serum NT-proBNP concentration was measured.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MVD (n = 119)</th>
<th>DCM (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>140 (39)</td>
<td>160 (63)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>35 (17)</td>
<td>33 (9)</td>
</tr>
<tr>
<td>Vertebral heart size</td>
<td>11.9 (1.3)</td>
<td>12.0 (0.9)</td>
</tr>
<tr>
<td>FS (%)</td>
<td>43.2 (11.6)</td>
<td>15.1 (6.8)</td>
</tr>
<tr>
<td>LAD:AoD</td>
<td>2.1 (0.6)</td>
<td>2.1 (0.6)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>145 (6)</td>
<td>146 (5)</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>110 (6)</td>
<td>111 (5)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.5 (0.6)</td>
<td>4.6 (0.4)</td>
</tr>
</tbody>
</table>

Data are given as mean (SD). FS = Fractional shortening. LAD:AoD = Ratio of left atrial dimension to aortic dimension.
DCM. Receiver-operating characteristic curve analysis revealed that serum NT-proBNP concentration could be used to distinguish dogs with cardiac disease (MVD or DCM) from healthy control dogs. Area under the receiver-operating characteristic curve was 0.92 (95% CI, 0.76 to 0.90; Figure 2), and a serum NT-proBNP concentration cutoff of 445 pmol/L had a sensitivity of 83.2% (95% CI, 75.9% to 89.0%), specificity of 90% (95% CI, 76.3% to 97.2%), positive predictive value of 96.6%, and negative predictive value of 61.0%. Twenty-two of the 23 (96%) dogs with cardiac disease that had a serum NT-proBNP concentration < 445 pmol/L had class I cardiac disease, and 1 had class II–compensated cardiac disease.

Serum NT-proBNP concentration and cardiac disease severity—Serum NT-proBNP concentration was correlated with physical, radiographic, and echocardiographic indicators of cardiac disease severity. Serum NT-proBNP concentration was significantly ($P < 0.05$) higher in dogs with MVD and a grade 5 cardiac murmur (median, 2,233 pmol/L; IQR, 1,361 to 3,647 pmol/L) than in dogs with MVD and a grade 3 or 4 cardiac murmur (median, 1,010 pmol/L; IQR, 556 to 2,538 pmol/L) or in dogs with MVD and a grade 1 or 2 cardiac murmur (median, 646 pmol/L; IQR, 369 to 3,007 pmol/L). Dogs with class II (median, 2,252 pmol/L; 1,056 to 3,544 pmol/L) or III (median, 2,279 pmol/L; IQR, 1,483 to 3,635 pmol/L) cardiac disease had significantly ($P < 0.001$) higher serum NT-proBNP concentrations than did dogs with class I cardiac disease (median, 618 pmol/L; IQR, 390 to 1,177 pmol/L; Figure 3).

Of the 137 dogs with cardiac disease, 58 had a serum NT-proBNP concentration > 1,725 pmol/L, and 49 had a serum concentration < 820 pmol/L. Receiver-operating characteristic curve analysis revealed that serum NT-proBNP concentration could be used to distinguish dogs with congestive heart failure (class II or III cardiac disease) from dogs without congestive heart failure (class I cardiac disease). Area under the receiver-operating characteristic curve was 0.83 (95% CI, 0.76 to 0.90; Figure 4). For dogs with cardiac disease, use of serum NT-proBNP concentration > 1,725 pmol/L as

![Figure 1](image1.png)

**Figure 1**—Box plots of serum NT-proBNP concentrations in 40 healthy control dogs, 119 dogs with acquired myxomatous MVD, and 18 dogs with idiopathic DCM. For each plot, the box represents the IQR, the horizontal line in the middle of the box represents the median, and the whiskers denote the range. Outlier values between 1.5 and 3 times the IQR are indicated by a small open square. *Significantly ($P < 0.001$) different from value for control dogs.

![Figure 2](image2.png)

**Figure 2**—Receiver-operating characteristic curve displaying sensitivity and specificity of using serum NT-pro-BNP concentration to distinguish healthy dogs from dogs with MVD or DCM. Various potential diagnostic cutpoints (pmol/L) are indicated along the curve. Area under the curve = 0.92.

![Figure 3](image3.png)

**Figure 3**—Box plots of serum NT-pro-BNP concentrations in 137 dogs with MVD or DCM grouped on the basis of cardiac disease class (class I, 60 dogs; class II, 30 dogs; class III, 47 dogs). Outlier values between 1.5 and 3 times the IQR are indicated by a small open square. Extreme outlier values > 3 times the IQR are indicated by a small black square. *Significantly ($P < 0.001$) different from value for dogs with class I cardiac disease.
indicative of congestive heart failure and serum NT-proBNP concentration < 820 pmol/L as indicative of an absence of congestive heart failure had a sensitivity of 88.2% (93% CI, 76.1% to 95.6%), specificity of 76.7% (93% CI, 63.6% to 87.0%), positive predictive value of 77.5%, and negative predictive value of 87.8%.

Bivariate regression analysis revealed that serum NT-proBNP concentration was positively correlated with heart rate (r = 0.413; P < 0.001), respiratory rate (r = 0.417; P < 0.001), vertebral heart size (r = 0.580; P < 0.001), ratio of left atrial dimension to aortic dimension (r = 0.546; P < 0.001), ratio of left ventricular dimension at end-diastole to aortic dimension (r = 0.438; P < 0.001), ratio of left ventricular dimension at end-systole to aortic dimension (r = 0.367; P < 0.001), BUN concentration (r = 0.207; P = 0.016), and serum creatinine concentration (r = 0.243; P = 0.004) and negatively correlated with serum chloride concentration (r = -0.270; P = 0.002). However, serum NT-proBNP concentration was not correlated with age, weight, serum sodium concentration, or serum potassium concentration. Multivariate regression analysis revealed that serum NT-proBNP concentration was significantly correlated with vertebral heart size (P < 0.001), serum creatinine concentration (P = 0.01), heart rate (P = 0.015), and ratio of left atrial dimension to aortic dimension (P = 0.013; serum NT-proBNP concentration = -5,422.8 + [589.6 x creatinine concentration] + [5.789 x heart rate] + [474.2 x left atrial-to-aortic dimension] + [392.6 x vertebral heart size]; R² = 0.377).

Median serum NT-proBNP concentration was significantly (P = 0.002) lower in dogs with class I cardiac disease (median, 351 pmol/L; IQR, 298 to 483 pmol/L) than in dogs with class II cardiac disease (median, 687 pmol/L; IQR, 431 to 1,585 pmol/L), and median serum NT-proBNP concentration was significantly (P = 0.018) higher in dogs with class II–active cardiac disease (median, 2,764 pmol/L; IQR, 2,018 to 3,682 pmol/L) than in dogs with class II–compensated cardiac disease (median, 1,456 pmol/L; IQR, 631 to 2,575 pmol/L). Also, median serum NT-proBNP concentration was significantly (P < 0.001) higher in dogs with an abnormal vertebral heart size score (median, 1,752 pmol/L; IQR, 733 to 3,066 pmol/L) than in dogs with a normal vertebral heart size score (median, 415 pmol/L; IQR, 351 to 649 pmol/L). Use of serum NT-proBNP concentration > 680 pmol/L to identify dogs with a vertebral size ≥ 11.5 was associated with sensitivity of 92.7% (93% CI, 83.4% to 96.5%), specificity of 67% (93% CI, 52.5% to 78.9%), positive predictive value of 80.9%, and negative predictive value of 85.7%. The area under the receiver-operating characteristic curve was 0.81 (95% CI, 0.73 to 0.89; Figure 5).

Discussion

Results of the present study suggested that serum NT-proBNP concentration was significantly different between healthy control dogs and dogs with cardiac disease, between dogs with cardiac disease with congestive heart failure and dogs with cardiac disease without congestive heart failure, and between dogs with cardiac disease and cardiomegaly (vertebral heart size ≥ 11.5) and dogs with cardiac disease without cardiomegaly. Previous studies1,4,6 have found that C-terminal BNP and NT-proBNP concentrations are high in dogs with heart disease and can be used to distinguish respiratory distress secondary to cardiac causes from respiratory distress secondary to noncardiac causes. Results of the present study expand on those findings by report-
ing results for a population of healthy dogs without any evidence of cardiac disease, proposing diagnostic cutpoints for distinguishing dogs with cardiac disease from those without and distinguishing dogs with more severe cardiac disease from those with less severe cardiac disease, and demonstrating correlations between serum NT-proBNP concentration and various radiographic and echocardiographic indices of cardiac disease severity.

In the present study, serum NT-proBNP concentration was significantly higher in dogs with MVD or DCM than in healthy control dogs, and receiver-operating characteristic curve analysis revealed that serum NT-proBNP concentration could be used to distinguish these groups. The high positive predictive value (96.6%) indicated that most dogs with a serum NT-proBNP concentration > 445 pmol/L truly had cardiac disease. The moderate negative predictive value (61.0%) indicated that some dogs with cardiac disease had concentrations lower than this cutoff (ie, a false-negative result). However, 22 of the 23 (96%) dogs with cardiac disease that had a serum NT-proBNP concentration < 445 pmol/L had class I cardiac disease. Both MVD and DCM progress along a continuum of decreasing function and increasing intracardiac pressures, and in the present study, serum NT-proBNP concentration was significantly lower in dogs with subclinical cardiac disease without radiographic evidence of cardiac enlargement (class Ia) than in dogs with subclinical disease with cardiac enlargement (class Ib). This suggests that serial testing may be useful in dogs suspected to have cardiac disorders, as initial negative results may eventually become positive as the disease progresses. However, specific longitudinal studies are needed to confirm this hypothesis.

Serum NT-proBNP concentration was correlated with several physical examination and clinical findings in the present study, indicating that measuring serum NT-proBNP concentration may be useful in assessing disease severity. For example, median serum NT-proBNP concentration in dogs with the loudest cardiac murmurs was 2 to 3 times the median concentration in dogs with moderate or soft murmurs. Similarly, median serum NT-proBNP concentration in dogs with congestive heart failure was > 3 times the median serum concentration in dogs without congestive heart failure. Moreover, serum NT-proBNP concentration was lower in dogs with class II cardiac disease in which treatment had resulted in an improvement in clinical condition (ie, class II–compensated) than in dogs with active class II cardiac disease. The latter finding suggests that the serum NT-proBNP concentration may decrease in response to treatment. If this can be verified in future studies, then serum NT-proBNP concentration may be helpful in assessing the response to treatment in dogs with congestive heart failure, as is reported for human patients with acute heart failure.20

Radiographic heart size is a useful index of disease severity in dogs with cardiac disease, and serum NT-proBNP concentration was correlated with radiographic heart size. A previous study26 classified dogs with vertebral heart size between 11.2 and 12.4 as having mild to moderate heart enlargement. In our experience, in dogs with MVD or DCM, signs of congestive heart failure are generally seen only when the vertebral heart size is ≥ 11.5. Thus, we sought to determine whether serum NT-proBNP concentration was useful in distinguishing dogs with vertebral heart size ≥ 11.5 from dogs with vertebral heart size < 11.5, and we found that a cutoff of 680 pmol/L could be used to distinguish these 2 groups. In contrast, although serum NT-proBNP concentration was positively correlated with echocardiographic left ventricular dimension and atrial dimension, receiver-operating characteristic curve analysis did not reveal any clinically useful cutoffs that could be used for these parameters. Nonetheless, our findings suggest that dogs with evidence of cardiac disease and serum NT-proBNP concentration > 680 pmol/L might benefit from further clinical investigation (eg, electrocardiography, radiography, or echocardiography) because the likelihood of clinically important cardiac disease in such patients in the present study was high.

Serum NT-proBNP concentration was significantly increased in dogs with congestive heart failure, compared with dogs with cardiac disease but without congestive heart failure; however, the clinical utility of measuring serum NT-proBNP concentration to identify dogs with congestive heart failure was limited by both false-negative and false-positive results. Reasons for this include the inexactitude of diagnostic tests used to identify congestive heart failure, particularly in geriatric dogs with concurrent respiratory disease; individual variations in serum NT-proBNP concentration; and the potential effect of various medications, such as diuretics, on serum NT-proBNP concentration. In the present study, there was an intermediate gray zone, such that serum NT-proBNP concentrations between 820 and 1,725 pmol/L could not be used to determine whether dogs had congestive heart failure. Similar findings were reported in a study19 involving 1,256 human patients with acute dyspnea in which 17% of the study population had NT-proBNP concentrations in an intermediate zone. Interestingly, other investigators20 have reported that patients with NT-proBNP concentrations in this intermediate zone had a higher mortality rate than did patients with lower values, regardless of whether they had cardiac or respiratory system disease. High C-terminal BNP concentrations have been reported in dogs with pulmonary hypertension,17 and additional studies involving dogs with primary pulmonary disease or mixed respiratory and cardiac disease are warranted.

Biological variation (ie, day-to-day variation and variation between animals) and use of assays with high coefficients of variation will confound interpretation of serum NT-proBNP concentration. An important limitation of the present study was that serum NT-proBNP concentration was measured only once in each dog. In humans, the day-to-day variation in NT-proBNP concentration among patients with stable cardiac disease can be as high as 50%,31 which would clearly influence interpretation of results. Possible causes of this variability include circadian patterns of secretion, differences in amount of physical exertion or fluid intake, and variations in clearance.31

Commonly used cardiac medications may also affect serum NT-proBNP concentration and may have
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altered our results. Dogs with cardiac disease in the present study were receiving a wide variety of drugs, including diuretics, angiotensin-converting enzyme inhibitors, β-adrenergic receptor blockers, vasodilators, positive inotropic agents, and antiarrhythmics, and we were unable to determine whether serum NT-proBNP concentrations were affected by these medications. This represents an important limitation of the present study. In particular, diuretic dose and timing of administration in relation to timing of blood sample collection would be expected to affect serum NT-proBNP concentration, as suggested by our results for dogs with class Ila and Iib cardiac disease. Metra et al30 reported that in humans, NT-proBNP concentration decreases within 24 hours after initiation of heart failure treatment and that the magnitude of the decrease could be used to predict which patients would survive or avoid rehospitalization during the subsequent 6 months. Additional studies are needed to evaluate the effects of various cardiac medications on serum NT-proBNP concentration in dogs.

In the present study, weak correlations were found between serum NT-proBNP concentration and BUN and serum creatinine concentrations (r = 0.207 and 0.243, respectively), which mirrors results in humans. However, we purposely excluded dogs with substantially impaired renal function (BUN concentration > 70mg/dL), and further studies involving dogs with severe renal insufficiency are needed.

In humans, C-terminal BNP and NT-proBNP concentrations are correlated with age, sex, ethnicity, and renal function.32,33 In contrast, in the present study, neither sex nor age was associated with serum NT-proBNP concentration, which was similar to results of previous studies.17,34 We did find that healthy purebred dogs had a significantly higher median serum NT-proBNP concentration than did healthy mixed-breed dogs. Thus, even though the difference was small, it is possible that serum NT-proBNP concentration is influenced by a combination of breed and disease. Baumwart et al35 reported that C-terminal BNP concentration was not high in Boxers with arrhythmogenic right ventricular cardiomyopathy, yet C-terminal BNP concentration is high in Doberman Pinschers with occult DCM.10 In contrast to findings of the present study, DeFrancesco et al36 reported that C-terminal BNP concentration was higher in dogs with DCM than in dogs with MVD or pericardial effusion. These differences between studies may reflect true biological differences in the production, release, and clearance of NT-proBNP between breeds or between diseases; differences between the 2 forms of BNP; or the relatively small number of dogs with DCM in the present study. Future studies targeting common breeds and diseases (e.g., Cavalier King Charles Spaniels with MVD or Doberman Pinschers with DCM) may result in breed- and disease-specific reference ranges and diagnostic cutoffs. Accordingly, findings of the present study represent general guidelines, and it is emphasized that serum NT-proBNP concentration should be used in conjunction with other diagnostic tests to achieve the most appropriate diagnostic and treatment plan.

In summary, results of the present study suggested that a serum NT-proBNP concentration > 445 pmol/L could be used to distinguish dogs with MVD or DCM from healthy dogs with a high positive predictive value. In addition, dogs with MVD or DCM that had a serum NT-proBNP concentration > 680 pmol/L were highly likely to have radiographic cardiomegaly (ie, vertebral heart size ≥ 11.5). Finally, dogs with MVD or DCM that had a serum NT-proBNP concentration > 1,725 pmol/L were likely to have congestive heart failure, whereas those with a concentration < 820 pmol/L were likely to not have congestive heart failure. Taken together, these findings suggest that measurement of serum NT-proBNP concentration may be a useful adjunctive clinical test for diagnosing cardiac disease in dogs and assessing the severity of disease in dogs with cardiac disease.

References


